24 February 2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for EU-M4All (Art 58) scientific opinion

Acoziborole Winthrop

international non-proprietary name: Acoziborole

Procedure No. EMEA/H/W/006686/0000

Note

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

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Table of contents

List of abbreviations

Abbreviation	Term
ACTH	adrenocorticotropic hormone
AE	adverse event
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	assessment report
ASAT	aspartate aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve extrapolated to infinity
AUC0-240	area under the concentration-time curve from 0 to 240 hours
AUC0-96	area under the concentration-time curve from 0 to 96 hours
BBB	blood brain barrier
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BMI	body mass index
BUN	Blood urea nitrogen
CAT	Committee for Advanced Therapies
CATT	card agglutination test for trypanosomiasis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	maximal concentration
CNS	central nervous system
CPCA	Carcinogenic Potency Categorization Approach
CPK	creatine phosphokinase
CPSF3	cleavage and polyadenylation specificity factor 3
CQA	Critical Quality Attribute
C-R	concentration-response
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
CTC	capillary tube centrifugation
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450
CYP	cytochrome P450
DBS	dried blood spot
DDI	drug-drug interaction
DEPT	Distortionless Enhancement by Polarization Transfer
DNDi	Drugs for Neglected Diseases initiative
DoE	Design of experiments
DRC	Democratic Republic of the Congo
DRC	the Democratic Republic of the Congo

DSC	Differential Scanning Calorimetry
DSMB	data safety monitoring board
DVS	Dynamic Vapor Sorption
EBE	empirical bayes estimate
ECG	Electrocardiogram
EMA	European Medicines Agency
Emax	Maximal effect
EoH	End of hospitalization (visit)
EOS	End of study
EOT	end of treatment
EP	evaluable participants
f_a	fraction absorbed
FaSSGF	fasted state simulated gastric fluid
FaSSIF	fasted state simulated intestinal fluid
FeSSIF	fed state simulated intestinal fluid
fm	fraction metabolized by CYP
GC	Gas Chromatography
GCP	good clinical practice
g-HAT	human African trypanosomiasis due to *Trypanosomia brucei gambiense*
GMR	geometric mean ratio
HAT	human African trypanosomiasis
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High performance liquid chromatography
HR	heart rate
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization
IPC	In-process control
IR	Infrared
KDIGO	Kidney Disease Improving Global Outcomes
KF	Karl Fischer titration
KPS	Karnofsky Performance Scale
LDPE	Low-density polyethylene
LLN	Lower limit of normal
LMP	Last menstrual period
mAECT	mini-anion exchange centrifugation test
Max	Maximum
MedDRA	medical dictionary for regulatory activities terminology
MIC	minimal inhibitory concentration to completely inhibit parasite growth
Min	Minimum
mITT	modified intention-to-treat
MO	Major objection

mRNA	messenger ribonucleic acid
NDMA	*N*-nitrosodimethylamine
NDMEA	*N*,*N*'-dimethyl-*N*,*N*'-dinitrosoethylenediamine
NECT	nifurtimox–eflornithine combination therapy
NLEM	non linear effect model
NMR	Nuclear Magnetic Resonance
NOR	Normal Operating Range
NTD	neglected tropical disease
OATP	organic anion transporting polypeptide
OC	Other Concern
PAR	Permitted Acceptable Range
PBPK	physiologically-based pharmacokinetic
PCR	polymerase chain reaction
PD	Pharmacodynamic
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PP	per-protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PSD	particle size distribution
PT	Preferred term
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
PXR	pregnane X receptor
QbD	Quality by design
QC	Quality control
QTcB	QT interval corrected according to Bazett'formula
QTcF	Fridericia´s corrected QT interval
QTPP	Quality target product profile
RDT	rapid diagnostic test
RH	Relative Humidity
r-HAT	human African trypanosomiasis due to *Trypanosomia brucei rhodesiense*
RMP	Risk management plan
RR	respiratory rate
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SDV	source data verification
SE	standard error
SEM	Scanning Electron Microscopy
SLS	sodium layril sulfate
SmPC	Summary of product characteristics
SOC	System organ class
T. b.	*Trypanosomia brucei*
$t_{1/2}$	half-life
TAMC	Total Aerobic Microbial Count

TDI	time-dependent inhibitor
TEAE	treatment-emergent adverse event
TGA	Thermogravimetric Analysis
tmax	Time to peak concentration
tmax	time to reach maximal concentration
TMDEA	Tetramethylethylenediamine
TSH	thyroid stimulating hormone
TSH	Thyroid stimulating hormone
TYMC	Total Combined Yeasts/Moulds Count
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
USA	United States of America
UV	Ultraviolet
V/*F*	apparent volume of distribution
VPC	visual predictive checks
WBC	white blood cells
WHO	World health organization
XRPD	X-ray Powder Diffraction
ΔHR	change in heart rate

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Acoziborole Winthrop
Active substance	Acoziborole
INN or common name	Acoziborole
Applicant	Sanofi Winthrop Industrie 82 Avenue Raspail 94250 Gentilly FRANCE
EMA product number	EMEA/H/W/006686
ATC code and pharmacotherapeutic group	<Not yet assigned> L2: p01antiprotozoals, L3: p01cagents against leishmaniasis and trypanosomiasis, L4: p01cx other agents against leishmaniasis and trypanosomiasis ()
Pharmaceutical form(s) and strength (s)	Tablet 320 mg
Packaging	blister (alu/alu)
Package size(s)	3 tablets
Route of administration	Oral use
Device or diagnostic	Not applicable
Orphan designation	N
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	EU-M4All scientific opinion
Legal basis	Article 58 of Regulation (EC) No 726/2004 (by analogy to Article 8(3) of Directive 2001/83/EC)
Indication	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).
New active substance status	Not Applicable

1.2. Scientific advice

Table 1. Scientific advice and protocol assistance

Date	Topic (quality / non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
19 November 2015	Non-clinical, clinical	EMEA/H/SA/3173/1/2015 /III	See below
26 July 2018	Clinical	EMEA/H/SA/3173/1/FU/1/ 2018/II	See below
19 September 2019	Quality	EMEA/H/SA/3173/2/2019 /I	See below
12 November 2020	Clinical	EMEA/H/SA/3173/1/FU/2/ 2020/PED/II	See below
24 June 2021	Non-clinical, clinical	EMA/SA/0000059280	See below
26 January 2023	Quality	EMA/SA/0000115465	See below

EMEA/H/SA/3173/1/2015/III

19 November 2015

SAWP Coordinators: Walter Janssens, Brigitte Blöchl-Daum

The Applicant received Scientific Advice on the development of SCYX-7158 for the treatment of human African trypanosomiasis (due to Trypanosoma brucei gambiense) from the CHMP on 19 November 2015 (EMEA/H/SA/3173/1/2015/III). The Scientific Advice pertained to the following non-clinical and clinical aspects:

- Adequacy of the completed non-clinical toxicological development to support a single-dose Phase 2/3 study and subsequent marketing authorization application according to Article 58 of EU Regulation 726/2004.
- Adequacy of the non-clinical and clinical safety evidence to support the use of a 960 mg single dose as the dose to be tested for the treatment of late stage human African trypanosomiasis; historical data for Nifurtimox-Eflornithine combination therapy as a comparator in the planned open-label clinical study; adequacy of preliminary efficacy results to support the efficacy assessment in adults and adolescents aged ≥15 years in the proposed indication.

EMEA/H/SA/3173/1/FU/1/2018/II

26 July 2018

SAWP Coordinators: Mair Powell, Hans Ovelgönne

The Applicant received Scientific Advice on the development of acoziborole (SCYX-7158) for the

treatment of human African trypanosomiasis (due to Trypanosoma brucei gambiense) from the CHMP on 26 July 2018 (EMEA/H/SA/3173/1/FU/1/2018/II). The Scientific Advice pertained to the following clinical aspects:

- Proposed reduction of sample size in the ongoing Phase 2/3 clinical study.

EMEA/H/SA/3173/2/2019/I

19 September 2019

SAWP Coordinators: Audrey Sultana, Finbarr Patrick Leacy

The Applicant received Scientific Advice on the development of acoziborole (SCYX-7158) for the treatment of human African trypanosomiasis (due to Trypanosoma brucei gambiense) from the CHMP on 19 September 2019 (EMEA/H/SA/3173/2/2019/I). The Scientific Advice pertained to the following quality aspects:

- Choice of starting materials for the manufacturing of acoziborole drug substance; commercial batch size and validation strategy; adequacy of the stability programme to support the proposed initial shelf-life and storage conditions.

EMEA/H/SA/3173/1/FU/2/2020/PED/II

12 November 2020

SAWP Coordinators: Anders Lignell, Mair Powell

The Applicant received Scientific Advice on the development of acoziborole for the treatment of human African trypanosomiasis (due to Trypanosoma brucei gambiense) from the CHMP on 12 November 2020 (EMEA/H/SA/3173/1/FU/2/2020/PED/II). The Scientific Advice pertained to the following clinical aspects:

- Proposal to conduct a Phase 3 open label, fasting pharmacokinetic, efficacy, safety, and tolerability study in children from 1 to 14 years of age with human African trypanosomiasis (Study DNDi-OXA-05-HAT).

EMA/SA/0000059280

24 June 2021

SAWP Coordinators: Dieter Deforce, Mair Powell and Markku Pasanen

The Applicant received Scientific Advice on the development of acoziborole for the treatment of human African trypanosomiasis (due to Trypanosoma brucei gambiense) from the CHMP on 24 June 2021 (EMA/SA/0000059280). The Scientific Advice pertained to the following non-clinical and clinical aspects:

- Omission of a non-clinical juvenile toxicity study.
- Adequacy of the proposed paediatric study to provide evidence for a comprehensive evaluation of acoziborole in patients from 1 to 14 years; adequacy of the updated PK data assessment approach from adults and children to define the dose recommendation in the paediatric population below 6 years of age; updated design of the paediatric clinical study in children from 1 to 14 years of age (Study DNDI-OXA-05-HAT) to support an extension of the

authorization to this paediatric age range (PK data handling approach for dose recommendation, choice of paediatric formulation, bioavailability of the paediatric formulation, sample size).

EMA/SA/0000115465

26 January 2023

SAWP Coordinators: Audrey Sultana, Sheila Killalea

The Applicant received Scientific Advice on the development of acoziborole for the treatment of human African trypanosomiasis (due to Trypanosoma brucei gambiense) from the CHMP on 26 January 2023 (EMA/SA/0000115465). The Scientific Advice pertained to the following quality aspects:

- Appropriateness of starting materials for the synthesis of acoziborole active substance with particular emphasis on the manufacturing control strategy including the control of the source of nitrosamine-based impurities.

1.3. Eligibility to the centralised procedure

The applicant Sanofi Winthrop Industrie submitted on 18 August 2025 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organization for Acoziborole Winthrop (Acoziborole).

The eligibility by the World Health Organization was agreed-upon on 17 October 2024.

Sanofi Winthrop Industrie (Acoziborole) will exclusively be intended for markets outside the European Union.

The applicant applied for the following indication: Acoziborole Winthrop is indicated for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic) human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* (g-HAT) in patients ≥ 15 years old. Acoziborole should be used in line with official recommendations.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

Article 58 (EU-M4All) of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 8(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant’s own tests and studies.

1.5. Information on paediatrics

Not applicable.

1.6. Applicant's request(s) for consideration

1.6.1. Accelerated assessment request

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

Treatment of both first stage (hemo-lymphatic) and second stage (meningo-encephalitic) of human African trypanosomiasis (HAT), or African Sleeping Sickness, due to Trypanosoma brucei gambiense (g-HAT) in patients ⩾ 15 years old. Pharmaceutical form: 320 mg tablets. Single oral dose of 960 mg. Despite efficacious available treatments for T. b. gambiense (NECT, fexinidazole), the claimed UMN and potential major therapeutic advantage for acozibrozole is acknowledged for patients 1) to be treated with NECT because of severe second-stage disease (one third of T. b. gambiense cases) considering the IV administration and the need for hospitalisation to receive it 2) receiving fexinidazole without extensive DOT (hospitalised) or have contraindications and those 3) unable to undergo lumbar puncture for disease staging. It is reasonable to expect that the remaining worldwide HAT cases could be effectively managed with a simple, well-tolerated oral therapy, improving accessibility and ease of treatment, even in remote areas.

Acoziborole is expected to provide major therapeutic advantage in terms of disease management/medical practice (no need for systematic CSF evaluation, hospitalisation, extensive DOT) and treatment consistency (ease of access, high adherence, better tolerability). Based on the potential for more consistent outcomes from the individual and the public health point of view, it is envisaged that acoziborole for T. b. gambiense treatment constitutes a major interest from the point of view of public health.

Considering the planned data packages; that over the years 2015-2023 the applicant sought several CHMP SA regarding quality, non-clinical and clinical aspects of the development of acoziborole; and the dossier includes 5 completed studies including 3 Phase I studies conducted in healthy adults (SAD, mass balance, DII), one Phase II/III pivotal study (DNDi-OXA-02-HAT) conducted in 208 g-HAT participants (adults and adolescents) to evaluate efficacy and safety of acoziborole, and a Phase II/III study placebo-controlled study in 1208 patients with not parasitologically-confirmed g-HAT for safety evaluation.

1.7. Steps taken for the assessment of the product

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

rapporteur:	Filip Josephson
Co-rapporteur:	Maria Grazia Evandri

The rapporteur and Co-rapporteur appointed by the PRAC were:

PRAC rapporteur:	Liana Martirosyan
PRAC Co-rapporteur:	Karin Bolin

The application was received by the EMA on	18 August 2025
An application for accelerated assessment was filed by the applicant. Accelerated assessment procedure was agreed-upon by CHMP on 24 July 2025	13 June 2025
The procedure started on	11 September 2025
The CHMP rapporteur's first assessment report was received on	11 November 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	13 November 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	18 November 2025
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP rapporteur and Co-rapporteur declared that they had completed their assessment report in less than 80 days	Not applicable
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	09 December 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	12 February 2026
The CHMP, in light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion for Acoziborole Winthrop on	24 February 2026

During the assessment of the application for a scientific opinion of Acoziborole Winthrop under Article 58 of Regulation (EC) No 726/2004 (i.e., EU-M4all), experts from the WHO and the national regulatory authorities of Angola contributed to the scientific discussions. The final scientific opinion was adopted by CHMP.

1.8. CHMP outcome

1.8.1. Opinion (positive)

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Acoziborole Winthrop is favourable in the following indication(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 CHMP, therefore, recommends the granting of the scientific opinion subject to the conditions described in the following sections.

1.8.2. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product

Characteristics, section 4.2).

1.8.3. Other conditions and requirements of the marketing authorisation

1.8.3.1. Periodic safety update reports

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 24 February 2026.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed.

1.8.4. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.4.1. Risk management plan (RMP)

The scientific opinion holder (SOH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.8.4.2. Additional risk minimisation measures

Prior to the launch of Acoziborole Winthrop in target countries, the scientific opinion holder 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 health care 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 scientific opinion holder 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:

Healthcare staff educational material:

- The Summary of Product Characteristics
- The Patient Card

- **Key messages of the 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 Human African Trypanosomiasis (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).

- **The patient information pack:**
- A Patient Leaflet
- A Patient Card – see description above

1.8.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic context

Aetiology

Human African trypanosomiasis (HAT) or sleeping sickness is a neglected tropical disease (NTD) that generally leads to the death of the patient if left untreated. The transmission of infective parasites to humans results from the bite of specific species of tsetse fly. Social and occupational factors may increase the risk of human contact with the vector e.g. proximity to river vegetation or dense forest.

Epidemiology

Two types of HAT are endemic in sub-Saharan Africa[1]:

- Gambiense HAT (g-HAT) is a chronic and slow-progressing form of the disease that lasts about 2 to 3 years and is endemic in West and Central Africa. Gambiense HAT is the predominant form of HAT (94% of HAT reported cases in 2024).

- Rhodesiense HAT (r-HAT) is an acute and fast-progressing form of the disease that lasts from weeks to months and is endemic in East and South Africa.

Humans are the main reservoir for *T. b. gambiense* parasites, whereas domestic and wild animals are the main reservoir for *T. b. rhodesiense* parasites.

In 2012, the World Health Organization (WHO) included the elimination of HAT as a public health problem by 2020 in its roadmap on NTDs. This is defined by <1 new case per 10 000 inhabitants per year in at least 90% of foci, with <2000 cases reported annually at the continental level. Thanks to several public health and vector control programmes and interventions, the incidence of g-HAT reported cases has dramatically decreased, reaching <1000 cases per year since 2018. Despite this, 5 affected countries (Democratic Republic of the Congo (DRC), Angola, Central African Republic, Congo, and South Sudan) have yet to achieve elimination at the national level, with DRC reporting the highest proportion of g-HAT cases in Africa (mean: 73% [range: 57% to 87%]), despite a >10-fold reduction in the number of reported cases over the past decade.

Pathophysiology

Two main clinical stages can be distinguished throughout g-HAT disease progression:

- First (haemo-lymphatic) stage:

Parasites are restricted to the blood and lymph, and cause nonspecific clinical signs and symptoms, such as headache, fever, weakness, and cervical adenopathy. This first stage may last for months to years. Patients often do not seek medical care and constitute a reservoir for disease transmission.

- Second (meningo-encephalitic) stage:

Parasites cross the blood-brain barrier (BBB) and invade the central nervous system (CNS). This advanced infection causes neurological signs and symptoms and psychiatric disorders, including delirium, disorientation, apathy, anxiety, emotional instability, abnormal speech, convulsions, seizures, and coma. Sleep disorder is a common sign of non-severe and severe second-stage disease.

Diagnosis

After a positive serological test detecting antibodies against *T. b. gambiense*, the diagnosis of g HAT disease is confirmed by the observation of trypanosomes (T+) in at least one body fluid, ie, blood, lymph, or cerebrospinal fluid (CSF).

The WHO criteria for staging g-HAT distinguish first (haemo-lymphatic), early second and late second (meningo-encephalitic) stages, diagnosis of the latter requiring (in addition to the presence of trypanosome in the blood or lymph) the presence of trypanosomes and/or WBC count >20 cells/µL in the CSF, thus necessitating a lumbar puncture.

[1] Updated figures for 2024 communicated by the WHO on 09 May 2025, ahead of their publication on the Global Health Observatory website.

Current therapies

Five pharmacological therapies are included in current WHO guidelines for the treatment of HAT[2].

Patient with g-HAT[1]	Clinical examination of g-HAT patients	Microscopic examination of CSF	Disease progression	Treatment[2]		
				1st line	2nd line	Rescue
<6 years or <20 kg	ns	≤5 WBC/µL No tryps	First stage	Pentamidine (IM)	ns	NECT (PO/IV)
		>5 WBC/µL Tryps+	Second stage	NECT (PO/IV)	Eflornithine (IV)	NECT long (PO/IV) or Melarsoprol (IV)
≥6 years and ≥20 kg	Non-severe disease	Not needed	First stage	Fexinidazole (PO)	***LP needed*** ↓ Pentamidine (IM) or NECT (PO/IV)	NECT or NECT long (PO/IV)
	Suspicion of severe disease[1] ***LP needed***	<100 WBC/µL	Non-severe second stage	Fexinidazole (PO)		
		≥100 WBC/µL or in failed LP	Severe[1] second stage	NECT (PO/IV)	Fexinidazole (PO)	NECT long (PO/IV) or Melarsoprol (IV)

Abbreviations: **CSF**, cerebrospinal fluid; **HCP**, health care professionals; **LP**, lumbar puncture; **NECT**, nifurtimox-eflornithine combination therapy total 10 days; **NECT long**, total 14 days; **ns**, not specified; **Tryps**, trypanosomes; **WBC**, white blood cells

Source: WHO 2024 guidelines.

- Diagnosis for g-HAT confirmed by the microscopic observation of trypanosomes (T_+) in blood, lymph, or CSF if LP is performed
- The main symptoms and signs consistent with severe meningo-encephalitic g-HAT are mental confusion, abnormal behavior, logorrhoea, anxiety, ataxia, tremor, motor weakness, speech impairment, abnormal gait, abnormal movements, and seizures. Sleep disorder is a common sign of non-severe and severe second-stage disease.

Most treatments require slow intravenous infusion or intramuscular injection. The negligible penetration of pentamidine through the blood brain barrier restricts its effective use to first stage disease and necessitates the use of lumbar puncture to determine disease progression if there is any suspicion of progression to second stage HAT. Mandatory lumbar puncture and hospitalisation for treatment pose significant clinical burdens/ barriers in the usual healthcare setting in Low- and Middle-Income Countries (LMIC).

The only available oral treatment is fexinidazole, which was granted a positive opinion on medicine for use outside EU in 2018 (EMA/CHMP/843546/2018). In 2022, fexinidazole was administered to 309/484 (64%) patients with g-HAT in the DRC[3]. Directly observed administration to ensure fed conditions and a change in dose on day 5 of 10, critical to achieving effective exposures, complicates this oral regimen, which furthermore is not recommended in severe second stage disease.

Acoziborole would fulfil an unmet medical need in g-HAT patients by simplifying and reducing the medical burden of treatment, being a single dose, oral treatment that can be administered for both first and second stage disease, negating the need for lumbar puncture.

[2] WHO Guidelines for the treatment of human African trypanosomiasis. Geneva, Switzerland. June 2024. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240096035
[3] WHO (World Health Organization). Report of the fifth WHO stakeholders meeting on gambiense and rhodesiense human African trypanosomiasis elimination, Geneva, 9 June 2023.

2.2. Aspects of development

The activity of acoziborole against *T. b. brucei* parasites was first demonstrated in *in vitro* in time-kill and reversibility studies and also in animal models of the disease.

The pharmacokinetic, pharmacology, and safety of acoziborole was evaluated in three Phase 1 clinical studies conducted in healthy adult male participants.

A pivotal Phase 2/3 efficacy and safety study (DNDi-OXA-02-HAT) has been completed in endemic countries (the DRC and Guinea) in adolescent (aged ≥15 years) and adult participants with g-HAT confirmed parasitologically.

Furthermore, the safety of acoziborole has been assessed in a different population (seropositive for g-HAT but not confirmed parasitologically) in a randomised, placebo-controlled Phase 2/3 study (DNDi-OXA-04-HAT) conducted in the same endemic countries.

At the time of dossier submission, one Phase 2/3 paediatric PK, efficacy and safety study (DNDi-OXA-05-HAT) and one Phase 3b safety study (STROGHAT) in adolescents seropositive for g-HAT but not confirmed parasitologically, are ongoing.

2.3. Description of the product

Acoziborole (also referred to as SCYX-7158 or AN5568) belongs to the family of benzoxaborole-6-carboxamides and is an antiprotozoal drug supplied as an uncoated, immediate-release tablet formulation of 320 mg strength (as used in the pivotal clinical study) and administered as a single oral dose in patients from 15 years of age. It has a long elimination half-life of 12.3 days.

This initial authorisation application seeks an indication for acoziborole for:

Treatment of both first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense (g-HAT) in patients ≥15 years old.

Acoziborole should be used in line with official recommendations.

The following posology is proposed:

Acoziborole Winthrop should be taken once as a single oral dose of 960 mg (three 320 mg tablets), with or without food.

Acoziborole specifically binds to and blocks the active site of the parasite enzyme named cleavage and polyadenylation specificity factor 3 (CPSF3), a metallo-β-lactamase that processes messenger ribonucleic acids (mRNA) and facilitates gene expression.

The mode of action of acoziborole thus differs from that of the nitroheterocyclic compounds nifurtimox and fexinidazole, which disrupt parasite deoxyribonucleic acid (DNA) integrity, and that of eflornithine which inhibits the enzyme ornithine decarboxylase involved in polyamine synthesis.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

Based on the review of quality data, the Rapporteur did not identify the need for a GMP inspection of the manufacturing sites included in this dossier.

2.4.2. Good laboratory practice (GLP) inspection(s)

All pivotal non-clinical studies are GLP. The Rapporteur did not identify any GLP issues.

2.4.3. Good clinical practice (GCP) inspection(s)

All studies presented in the dossier were conducted outside of the EU.

The Applicant states that study protocols were prepared in accordance with the general ethical principles set out in the Declaration of Helsinki and the International Council for Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (ICH E6) and submitted for approval by the Ethics Committee for Health Research in Central Africa (CERSAC), an independent institution common to several Central African countries, the Ethics Committee of the Ministry of Health in the Democratic Republic of the Congo (DRC) and of the National Ethics Committee for Health Research in Guinea.

The Applicant described in the dossier the mechanisms in place for study monitoring, to ensure the quality of study conduct and to check the accuracy and validity of data. Based on review of the data, no need for inspection was identified.

No inspection required.

3. Quality aspects

3.1. Introduction

The finished product is presented as tablets containing 320 mg of acoziborole as active substance.

Other ingredients are: calcium hydrogen phosphate dihydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycolate type A.

The product is available in polyamide/aluminium/PVC/PVDC/aluminium blister as described in section 6.5 of the SmPC.

3.2. Active substance

3.2.1. General information

The chemical name of acoziborole is 4-fluoro-*N*-(1-hydroxy-3,3-dimethyl-2,1-benzoxaborol-6-yl)-2-(trifluoromethyl)benzamide corresponding to the molecular formula $C_{17}H_{14}BF_4NO_3$. It has a molecular weight of 367.10 g/mol and the following structure:

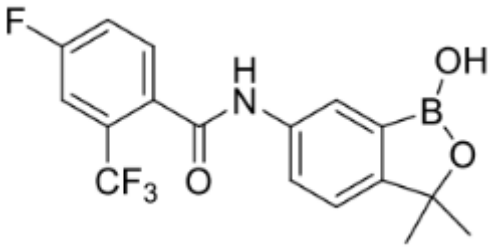


Figure 1: active substance structure

The chemical structure of acoziborole was elucidated by a combination of elemental analysis, infrared (IR) absorption spectrophotometry, ultraviolet-visible absorption spectrometry (UV-Vis), 1D-NMR (^{1}H, ^{13}C, DEPT), 2D-NMR (HSQC, HMBC), and high-resolution mass spectrometry (HRMS). The solid-state properties of the active substance were measured by X-ray single crystal diffraction, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), thermogravimetric analysis (TGA), scanning electron microscopy (SEM), particle size by laser diffraction and the specific surface area by BET analysis.

Acoziborole is a non-chiral compound presented as a white to off-white solid, which is slightly hygroscopic

Polymorphism is controlled as part of the active substance release and shelf-life specification.

Acoziborole is practically insoluble in water and buffers at relevant pH levels (1.2, 4.5 and 6.8). Based on its low solubility and high permeability, acoziborole is classified as a class II compound according to the Biopharmaceutical Classification System (BCS).

The dossier contains full information on the active substance.

3.2.2. Manufacture, characterisation and process controls

The active substance acoziborole is manufactured at two sites.

An acceptable QP declaration, based on on-site audits, concerning GMP compliance of both manufacturing sites has been provided.

The manufacturing process of acoziborole consists of a two branch convergent synthesis containing four synthetic steps, followed by a purification step using well defined starting materials with acceptable specifications. The manufacturing process is sufficiently described in the dossier.

Adequate in-process controls (IPCs) are applied during the synthesis. The IPCs employed in the process include reaction monitoring for each synthetic step.

The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable. Nonetheless, the specifications, should be updated to include an assay test. This is raised as a recommendation (REC 1).

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

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

The potential organic impurities which might form during synthesis as well as due to degradation of the active substance have been adequately discussed.

The specifications of the process intermediates contain several impurities that are not controlled in active substance and of which several are considered potentially mutagenic. Specification limits for these impurities have been adequately justified by spike/purge studies, demonstrating the capability of the manufacturing process to purge the impurities to acceptable levels in active substance.

Adequate control for the solvents used in the active substance synthesis is implemented in the process.

Screening for mutagenic impurities has been performed with one knowledge-based method and one statistical-based method in line with the requirements of ICH M7. The control strategy for potentially mutagenic impurities is acceptable.

The risk for contamination of the active substance with nitrosamine impurities has been assessed, and acceptable limits have been proposed for the control of two potential identified impurities. Following a major objection (MO) from the CHMP (MO1), the limit of one of the two impurities was revised. Confirmatory studies for the impurity have been performed and justified the omission of further testing.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. During the manufacturing process development several changes were made from process 1, used to manufacture batches of acoziborole active substance utilised in Phase I/II/IIIa clinical studies (i.e., COM.0836-10311-A and COM.0836-24715-B) to process 5, used to manufacture commercial scale batches. Changes introduced have been presented in sufficient detail and have been justified. A detailed discussion of each change made to the process has been provided and the impact of these changes on the quality of the active substance has also been discussed with no critical issue being identified. Batches used in clinical studies have been produced at different manufacturing sites than the routine commercial batches. A detailed discussion of each change made to the process has been provided and the impact of these changes on the quality of the active substance has also been discussed with no critical issue being identified. Comparability between the analytical methods used for analysis of earlier clinical batches and commercial batches has been adequately demonstrated.

The active substance is packaged in double low-density polyethylene (LDPE) bags, sealed with nylon ties, and placed in fiber drums. The grade of the LDPE material complies with the requirements of the European Pharmacopoeia Monograph 3.1.3 and EC food contact legislation.

3.2.3. Specification

The active substance specification includes tests for appearance, identification (IR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), polymorphism (XRPD), residue on ignition (Ph. Eur.) and water content (KF).

The selection of tests for the specification is based on ICH Q6A, pharmacopeial and regulatory guidelines such as ICH Q3A, Q3C, Q3D and M7.

The mutagenic impurities risk evaluation performed on the overall acoziborole manufacturing process results in the inclusion of one class 2and one class 3mutagenic impurities to be routinely controlled in the active substance. This control strategy as per ICH M7 allows to conclude that no apparent genotoxicity risk for humans can be associated with acoziborole.

Omission of control for benzene in the active substance specification has been properly justified.

Omission of testing of elemental impurities has been properly justified.

Omission of testing for active substance for microbiological contamination of the active substance in line with decision tree #6 of the ICH Q6A guideline have been justified.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification, assay, related substances method and the method for determining concentrations of one mutagenic impurity have been adequately characterized and described.

Batch analysis data from batches used for non-clinical and clinical studies as well as more recent production-scale batches have been presented. The results are within the specifications and consistent from batch to batch.

3.2.4. Stability

Stability data from three production scale batches of active substance from the proposed manufacturers stored in the proposed commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, assay, related substances, water content and polymorphism*.* The analytical methods used were the same as for release and were stability indicating.

All tested parameters remained within the specification limits for the duration of the study, with little or no change and no observable trends.

Forced degradation studies were also performed on one commercial scale batch. The active substance was exposed to elevated temperature. The mass balance was satisfactory for all tested conditions and the HPLC method for determining assay and related substances is considered stability-indicating.

The photostability of acoziborole has been tested on one primary stability batch in line with the requirements of the ICH Q1B guideline (not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter). The results demonstrate that acoziborole is a photostable compound.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when the active substance is stored in the proposed container closure system. The Applicant has presented a commitment to continue the stability studies past the currently proposed 24-month re-test period up to 60 months.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

The finished product consists of immediate release white to off-white oblong biconvex uncoated tablets (9 mm x 16 mm) debossed with 320 on one side.

The aim of the pharmaceutical development was to develop an immediate release oral solid dosage

form for acoziborole displaying satisfactory performance properties with regards to stability and ease of use in endemic countries where acoziborole will be administered. The quality target product profile (QTPP) (Table 2) was suitably defined based on the clinical and pharmacokinetic characteristics of acoziborole active substance as well as the dosage strength requirements for safe and effective therapy. The critical quality attributes (CQAs) were identified (Table 3).

Table 2. Quality target product profile (QTPP) for acoziborole 320 mg tablets

QTPP element	Target
Therapeutic indications	Human African Trypanosomiasis (HAT) due to Trypanosoma brucei gambiense
Route of administration	Oral
Dosage form	Immediate release (IR) tablet
Dosage strength	320 mg
Dose Regimen	3 tablets in a single intake (960 mg)
Dosage form attributes	White to off-white oblong biconvex tablet, 9 mm x 16 mm, debossed with 320 on one side
Shelf life and storage conditions	At least 3 years expected at 30°C/ 75% RH (zone IVb) in line with the WHO recommendations
Primary packaging	Blister aluminum/aluminum (Al/Al blister). No child proof resistance requested as the drug product will be administered under supervision of Health workers.

Table 3. Critical quality attributes of the finished product potentially impacted by formulation and/or process variables

Quality attribute	QTPP element	Target[a]	Assignment of criticality	Justification[a]
Appearance	Dosage form Dosage form attributes	White to off-white oblong biconvex tablet debossed with 320 on one side	Critical	Color, shape, dimension and appearance are usually not directly linked to safety and efficacy but are important for patient compliance. Thus, this CQA will be assessed throughout product and process development using risk assessment approach.
Assay	Dosage strength Shelf-life & storage conditions	95.0–105.0% of label claim	Critical	Assay variability (between batches) may affect directly safety and efficacy as it influences the dose the patient will receive. Formulation and process variables may affect the assay of the drug product. Thus, this CQA will be assessed throughout product and process development using risk assessment approach.
Uniformity of dosage unit (mass variation)	Dosage strength Dosage regimen	Conforms to Ph.Eur. 2.9.40 & USP <905>	Critical	Variability in content (between unit dose) may affect directly safety and efficacy as it influences the dose the patient will receive. Formulation and process variables may impact uniformity of dosage units. Thus, this CQA will be assessed throughout product and process development using risk assessment approach.
Dissolution	Drug delivery requirement Shelf-life & storage conditions	Report profile results	Critical	Consistent release of the product is required to demonstrate a robust process of the drug product. A slower dissolution may affect the bioavailability of the drug with a potential impact on efficacy. Formulation and process variables may impact drug product release. Thus, this CQA will be assessed throughout product and process development using risk assessment approach.
Degradation products (degradation/ impurity)	Dosage strength Primary packaging Shelf-life & storage conditions	Per ICH guidelines	Critical	Degradation products can impact safety and must be controlled based on compendial/ ICH requirements to limit patient exposure. Formulation and process variables can impact their level. Thus, this CQA will be assessed throughout product and process development using risk assessment approach.

a Target and justification set at the time of implementation of the Quality by Design approach.

Acoziborole is a poorly soluble substance and is proposed by the Applicant to be classified as a BCS class II active substance with low solubility and high permeability characteristics.

Polymorph is controlled by active substance specification. Polymorph is stable and remains unchanged through manufacturing and storage of the finished product.

The tablet strengths are qualitatively and quantitatively proportional in composition and the composition of the 320 mg tablet used throughout development, for Phase 2 to Phase 3 clinical studies, was retained as the proposed commercial formulation. For commercialization, final market image was defined and "320" was debossed on one side of the tablet.

The choice of the excipients and their function has been justified. The selection was based on their functionalities. No preservatives or antioxidants have been used. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The choice of excipients has been justified including a discussion on the need for any functionality-related characteristics. There are no novel excipients used in the finished product formulation.

No excipients of human or animal origin are used in the manufacturing of acoziborole 320 mg tablet. Therefore, no risk of contamination can be expected with regards to transmissible spongiform

encephalopathy agents or other contamination with adventitious agents.

Two oral dosage forms were developed and used in clinical studies: hard gelatine capsules (used in early Phase I clinical trials) and tablets (used in subsequent clinical trials). The relative oral bioavailability of the tablet versus capsule formulation was assessed and confirmed.

A standard manufacturing process is used to produce acoziborole 320 mg tablets.

To further assess the impact of the active substance particle size of the finished product properties, active substance batches were pooled by particle size population. No differences were observed on processability and finished product properties with the variation of acoziborole PSD and a limit for PSD in the active substance specification was considered unnecessary. The justification is further based on the active substance pharmacokinetic profile having a prolonged absorption window suggesting that the absorption is independent on the particle size in the finished product formulation. The pharmacokinetic profile is considered inconsistent with dissolution-limited absorption. Also, based on the manufacturing process, normalising any initial PSD variation and studies on batches manufactured with different PSD showing that the final finished product quality and performance are independent of starting PSD.

During formulation development a risk assessment was performed for each formulation variable that might have a critical impact on the critical quality attributes (CQAs) of the product. Early studies were performed on laboratory scale batches to investigate the impact of the excipients microcrystalline cellulose/calcium hydrogen phosphate dihydrate ratios and the granulation process parameters and the impact of levels of binder and disintegrant on the characteristics through a design of experiment (DOE) without claiming any design space.

The finished product is indicated for patients ≥ 12 years old. The suitability of the proposed formulation in the proposed age group has not been formally addressed in line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2. However, since the finished product is a common tablet formulation including commonly used excipients of no safety concern in the applied age group and adolescents are supposed to be able to swallow the tablets (oblong, sized 9 mm x 16 mm) the proposed finished product is considered acceptable. In addition, dissolution data has been presented to confirm that tablets can be crushed and swallowed with water for those patients not able to swallow the whole tablets as described in SmPC section 4.2.

The manufacturing development has been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. For better understanding the commercial process was developed following a Quality by Design (QbD) development strategy without the intention to seek for regulatory flexibility. No design space is applied for.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is a polyamide/aluminium/PVC/PVDC/aluminium blister. The material complies with Ph.Eur. and EU Regulation No. 10/2011 and amendments on plastic materials and articles intended to come into contact with food. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.3.2. Manufacture of the product and process controls

The finished product is manufactured at one site. This site is also responsible for batch release. For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The process is considered to be a standard manufacturing process. The manufacturing process and its control, as well as critical equipment have been described in the dossier.

Holding times (30 days) are proposed for final blend and bulk tablets in accordance with the EMA guideline on the manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015). The applicant confirmed that start of shelf life is defined in accordance with CPMP/QWP/072/96 EMEA/CVMP/453/01 CPMP/CVMP NfG on Start of Shelf-Life.

The process validation scheme submitted by the applicant is considered acceptable. The process will be validated prior to commercialisation by 3 consecutive batches at production scale.

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

3.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC), assay (HPLC), degradation products (HPLC), dissolution, uniformity of dosage units and microbiological purity (TAMC, TYMC, E. coli (Ph. Eur.).

The specification limits set are acceptable in line with ICH guidelines and Ph. Eur. and batch release data and stability data.

The tablet disintegration is controlled as an IPC. At release and shelf-life dissolution is controlled with appropriate limit and is considered to cover disintegration of the tablets. However, disintegration has not been studied in the stability studies. Since the dissolution method includes solubility agent (surfactant) due to low solubility of the active substance it is recommended that disintegration is studied in samples at the end of shelf life or even on expired batches. If results do not comply, a disintegration test should be added to the release- and shelf life specifications within a variation procedure and relevant corrective actions should be proposed. This issue is raised as a recommendation (REC2).

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data from 3 batches using validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

An acceptable risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Following a MO raised by CHMP (MO2), the risk of formation of one nitrosamine impurity and potential residuals of nitrites/nitrates present in the excipients have been addressed. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.3.4. Stability of the product

Stability data from 3 commercial scale batches of finished product from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (30ºC /75% RH) and for up to 6 months under accelerated conditions (40ºC /75% RH) according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The parameters tested are the same as for release with the addition of water content and XRPD. The analytical procedures used were the same as for release and were stability indicating as demonstrated through studies under forced conditions.

All tested parameters were well within the specifications. No significant changes have been observed regarding appearance, dissolution, assay, degradation products, water content, XRPD and microbiological examination.

Additionally supportive stability data on two clinical pilot scale batches stored at long term conditions (30ºC /75% RH) for 36 months and at accelerated conditions for 6 months (40ºC /75% RH) were provided. These batches have the same composition as the product proposed for commercialization but were produced by a different manufacturer with a potentially different manufacturing process (not described in detail). All parameters remained stable and within the specification as valid at the time. However, since these batches were analysed with different analytical methods and acceptance criteria for some tests: water content, assay, degradation products and dissolution, these data are considered only supportive and cannot be considered for the calculation of the shelf life.

Photostability testing following the ICH guideline Q1B was performed on one commercial scale batch. Results indicate that the product is not sensitive to light conditions tested.

Results under thermal and humidity stress conditions on one commercial scale batch were also provided. Under all conditions, the peak purity of acoziborole shows a purity angle below the purity threshold, indicating that the peak is pure and there is no interference from degradation products at the retention time of acoziborole. For all degradation conditions, the calculated mass balance results indicate that all impurities are detected, and no additional impurities are formed. The stability indicating nature of the methods was confirmed.

The provided stability results support a shelf life of 24 months without any temperature storage restriction. Also, it has been shown that the tablets are stable when exposed to light and humidity. The recommendation "to store below 30°C" has been proposed by the applicant to reflect the climatic zones of endemic countries where acoziborole Winthrop will be used. Clear storage recommendations (including temperature) in the product information will facilitate appropriate storage in the regions where the product, not intended for EU marketing, will be distributed by WHO. The proposed storage conditions "Do not store above 30 °C. Store in the original package in order to protect from light and moisture." is thus considered acceptable.

3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The MO raised by the CHMP on the originally proposed limit for one nitrosamine impurity and the risk of formation of another nitrosamine impurity and potential residuals of nitrites/nitrates present in the excipients (MO2) have been addressed. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the finished product. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the specifications of intermediates, and the recommendation to study disintegration in finished product samples at the end of shelf life or even on expired batches. These points are put forward and agreed as recommendations for future quality development.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. REC 1: The applicant is recommended to include a test for assay in the specifications of intermediates.
2. REC 2: The applicant is recommended to study disintegration in finished product samples at the end of shelf life or even on expired batches. If results do not comply a disintegration test should be added to the release- and shelf life specifications via a variation procedure and relevant corrective actions should be proposed.

4. Non-clinical aspects

4.1. Introduction

The non-clinical dossier for acoziborole contains sections for (non-clinical) pharmacology (section 5.3) – with primary pharmacodynamics covered by Clinical sections – pharmacokinetics/ADME (ncPK, section 5.4.) and human toxicology (section 5.5., including an assessment for environmental risk based on the European (EMA) guidelines).

4.2. Analytical methods

The non-clinical dossier involves analytical methods (LC-MS/MS methods), primarily used for the analyte measurements of acoziborole and its metabolite SCYX-3109 (also known as M9) in plasma samples from rats, rabbits, and dogs. The sample matrix used was acidified plasma, except for some

studies/methods which used plasma with K2EDTA. The lower limit of quantification (LLOQ) was 25 ng/mL for acoziborole and 10 ng/mL for SCYX-3109, except for the 13-week toxicity studies where the LLOQ was 20 ng/mL and 5 ng/mL, respectively. They analytical methods have been found to be adequate for their intended purpose and have been sufficiently validated. When relevant, compliance with Good Laboratory Practice (GLP) has been ensured. Incurred sample reanalysis (ISR) was performed and reported in all GLP studies, except in reproductive toxicity studies.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

See Clinical section.

4.3.1.1. Secondary pharmacodynamics

The secondary pharmacodynamics section encompasses one experimental study on enzyme- and radioligand binding assays for a total of 43 enzymes and with 68 transporters, ion channels, and receptors (tested at 10 µM concentration). No tested protein demonstrated ≥50% inhibition or stimulation. The maximum interaction/protein inhibition at 10 µM was at 37% for human CYP2D6 followed by human Adenosine A3 receptor at 31% and human HIPK2 at 28%.

4.3.2. Safety pharmacology

The Safety pharmacology section included four dedicated in-vivo studies (cardiovascular, respiratory, nervous system/behaviour, and gastro-intestinal motility) and one in-vitro study (hERG assay). The hERG study indicated that acoziborole may have some weak hERG channel inhibition functionality (the hERG assay with 10 to 100 µM exposure gave an extrapolated IC50 at 135.4 µM) but the IC50 is estimated to be 127x higher than the clinical unbound Cmax at the therapeutic dose of 960 mg. An in-vivo telemetry-based dog study using a repeated single dose-escalation design (vehicle + 48h + 5 mg/kg + 21d washout + 15 mg/kg + 21d washout + 40 mg/kg + 24h observation) did, although based on a low number of animals (n=4), not detect any changes in cardiovascular parameters – an outcome also supported by the general toxicity studies in dog with up to 13w exposure and using electrocardiogram measurements (see also Discussion). It can be noted that based on the toxicokinetics measurements in the 14d-to-28d toxicity dog study, a NOAEL of 40 mg/kg would roughly correspond to a Cmax of 12.8 µg/mL and a AUC0-24h of 242 µg × h/mL.

No acoziborole changes were seen in the respiratory function or nervous system/behavioural traits in Sprague Dawley male rats at 15 or 40 or 80 mg/kg single oral gavage doses (NOAEL 80 mg/kg). Based on D1 toxicokinetics measurements in the 28d general toxicity study in Sprague-Dawley rat (see Toxicology section), this NOAEL would roughly correspond to Cmax 42.1 µg/mL and AUC0-24h 844 µg × h/mL. In the toxicity studies (see Toxicology section) both rat and dog manifested gastrointestinal toxicity. In a single oral dose exposure of adult male & female Wistar rat at 50 or 140 or 400 mg/kg, there were no effects on gastrointestinal motility (within 1-2h post-dose, giving a NOAEL of 400 mg/kg).

4.3.3. Pharmacodynamic drug interactions

See 5.2.2.11. Pharmacokinetic interaction studies, below.

4.4. Pharmacokinetics

4.4.1. Absorption

Nonclinical studies of acoziborole were conducted in mice, rats, dogs, and monkeys to characterize absorption, systemic exposure, and the influence of dose and formulation. In mice, the time to reach maximum plasma concentration (tmax) following oral administration ranged from 0.5 to 6 hours. Maximum plasma concentrations (Cmax) and overall exposure (AUC) increased approximately dose-proportionally between 13.4 and 39.9 mg/kg. Absolute bioavailability (F) varied with formulation, ranging from 54.5% at 13.4 mg/kg using 5% dextrose, decreasing to 45.3% at 26.2 mg/kg with the same vehicle, and increasing to 71% at 39.9 mg/kg when 2% ethanol was added to improve solubility. Intraperitoneal administration at 39.9 mg/kg produced similar Cmax and AUC values as oral dosing at the same dose.

In rats, tmax ranged from 2 to 8 hours following oral administration and generally increased with dose (3–30 mg/kg). Plasma exposure, including both Cmax and AUC, increased roughly proportionally with dose. Absolute bioavailability was approximately 53% at 8.86 mg/kg using a solubility-enhancing vehicle, while a higher dose of 26.8 mg/kg with a dextrose formulation resulted in slightly lower-than-expected exposure, likely due to limited solubility.

In dogs, tmax was markedly longer, ranging from 17 to 32 hours, and some studies showed multiple peaks in plasma profiles. Cmax and AUC increased roughly dose-proportionally up to 23.5 mg/kg, whereas higher doses showed less than proportional increases, likely reflecting limited dissolution or absorption. Bioavailability using the formulation employed in toxicology studies ranged from 59% to 100%.

In monkeys, an oral dose of 10.4 mg/kg resulted in tmax around 9.5 hours and high bioavailability of 88.5%. Penetration across the blood-brain barrier was demonstrated, with cerebrospinal fluid (CSF) levels corresponding to approximately 3.9% of plasma exposure, consistent with the free fraction in plasma.

Overall, these data suggest that absorption is solubility-limited, that solubilizing vehicles improve systemic exposure.

4.4.2. Distribution

Acoziborole is highly bound to plasma proteins across all species, including humans, with binding ranging from 94% to 98%, resulting in a low free fraction of approximately 2–5%. Tissue distribution studies demonstrated wide distribution, with the highest levels observed in the liver, thyroid, kidney, and subcutaneous fat, while brain and eye exposure was lower. CNS penetration was confirmed in monkeys, with cerebrospinal fluid concentrations corresponding to the free fraction in plasma, indicating that unbound drug can reach the brain. Tissue half-lives were prolonged, particularly in female rats, where plasma radioactivity persisted for up to 168 hours post-dose. Placental transfer and excretion into milk were demonstrated in rats, indicating potential foetal and neonatal exposure. No significant melanin binding was observed.

Human data show an apparent volume of distribution of approximately 109 liters, and CNS exposure is

consistent with predictions based on the free plasma fraction.

Overall, distribution is broad, with high exposure in target organs, and systemic exposure appears sufficient to support translational relevance of nonclinical findings.

4.4.3. Metabolism

Acoziborole exhibits high metabolic stability across species. In vitro studies in liver S9 fractions, microsomes, and primary hepatocytes from mouse, rat, dog, monkey, and human indicated low intrinsic clearance and half-lives exceeding 350 minutes. The primary metabolic pathway involves oxidative deboronation followed by glucuronidation to form metabolites M9 and M4, which were consistently observed in all species except for minor metabolites such as M5, M7, M8, and M10, which were only detected in dog or monkey hepatocytes.

In humans, no major metabolites were detected, with over 95% of circulating compound present as unchanged parent drug. The metabolic profile in nonclinical species was generally predictive of human metabolism, with no evidence of human-unique metabolites, suggesting low clinical relevance of minor species-specific metabolites.

Overall, acoziborole shows very limited metabolism, and nonclinical models are considered appropriate for predicting human metabolic patterns.

4.4.4. Excretion

Excretion of acoziborole occurs primarily via the faecal route, with minor renal elimination. In rats, approximately 66–73% of the dose was recovered in feces, and 13–20% in urine within 14 days after oral administration. Long terminal half-lives were observed across species, with values ranging from 21.4 hours in monkeys to 26.7 hours in mice and 23.9–28.5 hours in rats. In dogs, half-lives ranged from 25.7 hours to 100 hours, although the longer value was considered an outlier. Biliary excretion in dogs was minimal (<1% of dose over 48 hours) and administration of activated charcoal at low doses of acoziborole reduced the half-life by approximately 50%, suggesting possible enterohepatic recirculation; the relevance of this mechanism in humans is uncertain. There is no elimination data in dogs presented.

Human pharmacokinetics demonstrate an extremely long apparent half-life (~296 hours), which is consistent with slow absorption, extensive tissue distribution, and minimal metabolic clearance.

Overall, excretion appears to be characterized by metabolic stability, low clearance and hepatobiliary excretion. Enterohepatic recirculation could to some extent contribute to the prolonged half-life.

4.4.5. Pharmacokinetic drug interactions

See 5.2.2.11. Pharmacokinetic interaction studies, below.

4.4.6. Other pharmacokinetic studies

N/A.

4.5. Toxicology

All toxicological studies used an oral gavage exposure route in order to represent the clinical administration route. The vehicle used in the formulation in all animal studies was 0.5% (w/v) Methyl cellulose & 0.1 % SDS in water.

4.5.1. Single-dose toxicity

Two acute toxicity studies (non-GLP) have been conducted in rats. One of the studies was a dose-escalation study (starting at 100 mg and increasing up to 800 mg/kg). Animals started to manifest reduced food-intake after 100 mg/kg, adverse clinical signs after 400 mg/kg and started to die after 800 mg/kg, possibly due to gastrointestinal toxicity. Female rats were somewhat more sensitive than male rats. In the other rat study (50 and 200mg/kg groups, single dose followed by 21d observation), there were adverse clinical signs and BW reduction at 200 mg/kg. Haematological effects at 50 mg/kg (decrease in WBC and basophiles, in increase in reticulocytes) but more pronounced haematological effects at 200 mg/kg.

4.5.2. Repeat-dose toxicity

The general toxicity/repeat-dose toxicity studies used rat and (Beagle) dog as animal models. Both rat and dog contain the minor metabolite SCYX-3109 which has also been found in humans. The SCYX-3109 was shown to be pharmacologically inactive against S427 strain of Trypanosoma brucei. For rat, the evaluations included: a 7d RDT study (non-GLP), followed by GLP compliant 28 d and 13 w RDT studies. The No Observed Adverse Effect Levels (NOAELs) for the 28d and 13w rat studies was 5 mg/kg (LOAELs 15 mg/kg). In the dog, general toxicity was evaluated in a 7d RDT studies (non-GLP) at 5 to 50 mg/kg), and in GLP compliant 28 day and 13 w RDT studies evaluating 5-40/15 mg/kg, and 5-20 mg/kg, respectively. The NOAEL for the 28d study was <5mg/kg (Lowest Observed Adverse Effect Level, LOAEL 5 mg/kg) and for the 13w study 20 mg/kg.

Mortality & moribundity: Unscheduled deaths were seen in the repeat-dose toxicity rat studies (and the rabbit EFD study). In the 28d rat study, rats had unscheduled deaths at 80 mg/kg and manifesting clear signs of gastrointestinal toxicity (e.g., superficial mucosal necrosis, single cell necrosis in the glandular epithelium of stomach, single cell necrosis of intestinal crypt epithelium, reduced number of crypts, vacuolation of the enterocytes and lymphoid depletion in the Peyer's patch of intestinal segments). There were no unscheduled deaths in the 13w rat study.

Clinical signs, body weight & food-intake: Across studies, at higher doses, rats manifested a set of shared clinical behavioural signs (e.g., hypoactivity, dehydration, abnormal gait, hunched posture). In the 28d+28d rat study, these clinical signs were present at ≥40 mg/kg (but reversible). In a single dose study (followed by 15d observation), red eye discharge was observed at 400 mg/kg which was linked to uveitis/keratitis. After 13w exposure, rats manifested thinness and hypoactivity at the high dose (30 mg/kg) but with subsequent recovery. For dogs, after 14d-to-28d exposure, the animals manifested hypoactivity and emesis at ≥15 mg/kg and abnormal gait, dehydration, conjunctivitis and diarrhoea at 40 mg/kg. No adverse clinical signs except diarrhoea at the maximum dose of 20 mg/kg were seen in the 13w dog study. After 28d exposure in rats, body weight and food-intake reduction (>10%) was seen at ≥40 mg/kg. In the 13w rat study, body weight reduction was seen at 30 mg/kg. After 14d-to-28d exposure in dogs, the bodyweight was decreased at ≥15 mg/kg (up to -20% reduction). This correlated with a reduction in food-intake. There was no body weight or food-intake change after 13w exposure up to the maximum dose 20 mg/kg. Overall, with regard to adverse clinical signs and reduced body weight & food-intake, the data indicates that rats, in sub-chronic exposure

settings, begin to be sensitive at 30 to 40 mg/kg whereas dogs have a range of 15 to 20 mg/kg. Generally, these effects were partially or fully reversible.

Digestive system - salivary glands: In a 28d rat study, salivary glands manifested atrophy at 80 mg/kg (not seen after 28d recovery). In some animals, the salivary gland changes were characterized by smaller acini, single cell necrosis of glandular cells and/or decreased granules of the duct epithelium.

Digestive system - stomach: In the non-clinical pharmacokinetics distribution rat study, the highest levels of radioactivity (AUClast ratio vs plasma >1.4) were located to the GI tract (stomach and small intestine mainly). In the 100-to-800 mg/kg dose-escalation rat study, glandular stomach ulcers were detected at ≥400 mg/kg. In a 7d rat study, at ≥140 mg/kg, the glandular stomach showed superficial mucosal necrosis. In the 28d rat study, one could also observe mucosal necrosis, single cell necrosis in the glandular epithelium of stomach at 80 mg/kg (only in animals that had unscheduled deaths). No similar effects were seen in the 13w rat study (maximum dose 30 mg/kg). In the 14d-to-28d dog study, the stomach had dilated/cystic glands at ≥5 mg/kg with increased mucus secretion at 40 mg/kg (not seen in recovery animals). No similar outcomes were seen after 13w exposure (maximum dose 20 mg/kg).

Digestive system - intestines: At 800 mg/kg in the dose-escalation rat study, there was a reddish discoloration of ileum and jejunum and also crypt epithelial apoptosis. After 7d exposure, at ≥140 mg/kg, rats manifested single cell necrosis, crypt epithelium, crypt epithelial hyperplasia and villous atrophy or blunting in the duodenum, jejunum and ileum. The colon had mucosal single cell necrosis, mucosal hyperplasia and mucosal atrophy. After 28d exposure in rat, crypt epithelial hyperplasia & single cell necrosis was present at 80 mg/kg in duodenum, jejunum, ileum, cecum and rectum (not seen in recovery animals). No similar effects were seen in the 13w exposure rat study. In dogs, in a safety pharmacology dog study (single dose: 50, 140 or 400 mg/kg) for gastro-intestinal motility (based on charcoal travel-distance in the intestines), there were no motility changes (NOAEL 400 mg/kg). After 28d repeat-dose exposure in dogs, one could detect dilated/cystic gland(s) at ≥15 mg/kg in the duodenum, jejunum, ileum, and cecum. There was also necrotizing inflammation in the duodenum at 40 mg/kg (1/6 animals). This was possibly correlated with a reduction with total protein and albumin levels at ≥15 mg/kg. These effects were not seen in recovery animals. No similar GI-tract effects were seen in the 13w+6w dog study. It can be noted that rabbits (females in the rabbit EFD study) manifested GI-tract toxicity at 25 mg/kg (the intestines of some of the animals with unscheduled deaths had a dark liquid content).

Digestive system - hepatobiliary: Liver toxicity was seen in both rats and dogs. After 7d daily exposure in rats, at ≥140 mg/kg, the liver manifested hepatocellular hypertrophy, single cell necrosis, hepatocyte and hepatocyte vacuolation. After 28d exposure, increased liver weight was seen ≥15 mg/kg and hepatocellular hypertrophy & sinusoidal single cell necrosis at ≥40 mg/kg. There was also a 7-8x increase in the GGT biomarker at 80 mg/kg. In the 13w exposure rat study, total bilirubin levels increased at ≥5 mg/kg and liver weight increased at ≥15 mg/kg. These effects were not seen in recovery animals. In the 14d-to-28d dog study, the liver had minimal to mild cytoplasmic rarefaction in hepatocytes at ≥15 mg/kg. Females had also a minimal glycogen depletion in hepatocytes at ≥15 mg/kg. These effects were not seen in recovery animals. No liver effects were seen in the 13w dog study (maximum dose of 20 mg/kg).

Digestive system - pancreas: After 28d exposure in rats, acinar cell vacuolation is seen at 40 mg/kg but not 80 mg/kg. In the 13w rat study, acinar cell vacuolation was present at 15 & 30 mg/kg (up to severe levels at 40 mg/kg). This was not observed in the 28d recovery animals but there was only partial recovery after 13w exposure.

Cardiophysiological effects: The hERG in-vitro safety pharmacology study (concentrations 10-100µM) indicated a potential weak hERG inhibition effect (IC_{50} 135.4 µM) but a dedicated dose-escalation study

in telemetered dogs (from 5 to 15 to 40 mg/kg) did not detect any changes in systolic-, diastolic-, mean blood pressure, heart rate, or QT intervals. Electrocardiogram observations in the pivotal repeat-dose toxicity studies (up to 40 mg/kg) did also not detect any signs of physiological cardiotoxicity.

Adrenal glands: The adrenal glands manifested cortical hypertrophy in the dose-escalation rat study at the maximum dose of 800 mg/kg. After 28d exposure, the adrenal weight was increased at ≥15 mg/kg coupled with cortical hypertrophy in the Z. fasciculata at 40 mg/g. After 13w exposure, the adrenal weight was increased at 30 mg/kg (mainly in males) and there were up to moderate levels of cortical vacuolisation at ≥5 mg/kg. Based on electron microscopy, the vacuolisations likely represent cytoplasmic lipid accumulation. The adrenal effects were partially reversible in rats. In the 14d-to-28d dog study, adrenals had also cortical hypertrophy at ≥5 mg/kg (not reversible at 15 & 40 mg/kg after 42d recovery, not affected in the 13w dog study). The toxicological impact of vacuolisation is unclear and the clinical relevance of the effects on the adrenal glands is also uncertain.

Male reproductive organs: Based on the general toxicity studies, male reproductive organ effects were seen in both rats and dogs. In rats, after 28d exposure, at ≥40 mg/kg, there was degeneration in seminiferous tubules & decreased cytoplasm in Leydig cells. At 80 mg/kg, there was a reduction in testis weight. In the epididymides, there was cellular debris in the duct lumen at ≥40 mg/kg and oligospermia & single duct cell necrosis & duct cell vacuolation at 80 mg/kg. Additional male reproductive organs (seminal vesicles and the prostate) manifested atrophy at 80 mg/kg. In the 13w exposure rat study (with 5 to 30 g/kg doses, but only exposure every second day after d40-d42), no controls but a few males in every exposure group had small testis although the link to drug exposure is uncertain. Minimal to moderate degeneration of seminiferous tubule was also seen in some animals at 30 mg/kg (with low and mid-doses and recovery animals not investigated). In the epididymides, minimal to mild sperm granuloma and minimal to moderate spermatid depletion were detected at ≥15 mg/kg (also present in recovery animals). In the 14d-to-28d dog study, the weights of the testes, epididymides and prostate were reduced at 40 mg/kg (although without underlying histopathological lesions). The testes were bilaterally small in 1/3 main study dogs at 40 mg/kg (effects not seen in the single recovery male) – which may or may not be due to the immaturity of the dogs (the animals were 6-7 months old, and puberty usually occurs between 6-9 months in Beagle dog). In the 13w+6w dog study, there were also some testes effects although without clear dose-response. There was vacuolation in seminiferous tubule (minimal to mild) at 10 mg/kg (2/3 animals) and 20 mg/kg (1/3 animals) plus mild degeneration in seminiferous tubule at 10 mg/kg only (1/3 animals). These effects were not seen in recovery animals. As similar histopathological signs were seen in rat, the findings in the 13w+6w dog study cannot be dismissed.

Female reproductive organs: In the 28d daily exposure rat study, atrophy was observed in the mammary glands, ovaries (intestinal cell atrophy), uterus and vagina at 80 mg/kg (not seen in 28d recovery animals). No similar effects were seen in the 13w+6w rat study or the dog studies.

Haematological toxicity: Exposure of both rat and dog seems to generate anaemic conditions. After a single dose at 200 mg/kg, rats manifest an increase in reticulocytes that remains over 21d. In a 7d daily exposure rat study, females manifested dose-dependent haematological toxicity with eosinophil reduction, bone marrow hypocellularity, lymphoid depletion in thymus or spleen at ≥50 mg/kg and males at 140 mg/kg. After 28d exposure in rat, medullary haematopoiesis in the spleen and reticulocytes and hypochromic cells increased at ≥5 mg/kg. Spleen weight increased while red blood cells decreased at ≥15 mg/kg. Decreased red pulp cellularity and hypocellularity in the femur and sternum was seen at 80 mg/kg. After 13w exposure, spleen weight increased at ≥5 mg/kg. This correlated with increased (minimal to mild) cellularity/red pulp. Increase of haematopoietic cells was seen 30 mg/kg. There were no effects on the bone marrow after 13w exposure. Overall, these effects were reversible.

Lymphoid system & immunotoxicity: After a single dose at ≥50 mg/kg, male rats manifested a reduction in white blood cells (between -27% to -66%, including leukocytes, monocytes, basophiles) which spans the full observation period (21d). At higher repeated doses in rats (≥140 mg/kg) there were signs of reduced white blood cell counts. In dogs, this was seen at ≥15 mg/kg after at least 14d to 28d exposure. After 28d exposure in rats at the maximum dose of 80 mg/kg, lymphoid depletion is seen in lymph nodes, spleen and thymus but there were no clear changes in the white blood cell count. After 13w exposure in rats (mostly every second day exposure), there was no similar effects or white blood cell changes. In dogs, after 14d-to-28d exposure, there was thymus weight reduction – attributed to lymphoid depletion at the ≥5 mg/kg (low dose) and the white blood cell count was also reduced (roughly -50%) at ≥15 mg/kg (mid-dose) with lymphoid depletion sins in the spleen at 40 mg/kg (high dose).

Other toxicity: There were no ophthalmological adverse effects in the animal studies but in a single dose rat study (followed by 15d observation), at 400 mg/kg there were signs of uveitis/keratitis in some animals. After 28d exposure in dogs, transient congested conjunctiva was seen at 40 mg/kg. After 28d exposure in rat, the skin had a thin epidermis, decreased sebaceous glands, and atrophic hair follicles at 80 mg/kg (not seen in recovery animals). 28d exposure in dogs generated follicular cell hypertrophy at 40 mg/kg only in females.

4.5.3. Genotoxicity

Acoziborole was negative in Ames test, positive in the in-vitro micronucleus test (absence of rat S9, 3h exposure) but negative in the in-vivo micronucleus rat study (oral gavage doses for two days between 100 and 400 mg/kg, assessment of femur bone marrow, TK evidence of systemic exposure of parent compound and the SCYX-3109 metabolite). Overall, based on the evidence, acoziborole is considered non-genotoxic.

4.5.4. Carcinogenicity

Due to the indication (single dose), no carcinogenicity studies have been conducted.

4.5.5. Developmental and reproductive toxicity

Rat and rabbit were used as animal models in a standard DART package (rat FEED study, rat and rabbit EFD studies, rat PPND study; see also Reproductive organ toxicity in the Repeat-dose toxicity section). No juvenile toxicity studies have been conducted (see Discussion below).

FEED: A male & female rat FEED study (5, 15 and 25 mg/kg) has been conducted (exposure of males 28d prior to mating plus a maximum of 3w; exposure of females 14d prior to mating and until GD7 in pregnant females – with the pregnant females terminated on GD13 to GD16). While there were reproductive organ toxicity findings in the repeat-dose toxicity rat studies (including signs of oligospermia), there were no adverse effects on reproductive functionality or on early embryogenesis so the reproductive NOAEL was at 25 mg/kg. General adversity (body weight/gain reduction) was present in females as a trend at 5 mg/kg and more clearly at ≥15 mg/kg with adverse clinical signs at the high dose 25 mg/kg. As such, the more general parental NOAEL in the FEED study is 5 mg/kg.

EFD: Daily oral exposure (5, 15 & 25 mg/kg) of rats (GD6 to GD17) generated maternal toxicity and embryofoetal growth retardation (BW-reduction and delayed skeletal ossification/slight increase in skeletal variations) at 25 mg/kg. The NOAEL is set at 15 mg/kg (LOAEL 25 mg/kg). In daily orally exposed pregnant rabbits (at 5, 15 and 25 mg/kg, between GD6 to GD19, termination on GD29), at ≥5

mg/kg, there was an increase in females with resorptions and post-implantation loss. Regarding malformations, there were more malformations at 25 mg/kg with a possible trend of increase at 15 mg/kg (in controls there was 1 malformations (in 1 litters), at 5 mg/kg 0(0), at 15 mg/kg 2(2) and at 25 mg/kg 5(4) – which corresponds to a total of 1/186 foetuses, 0/150, 2/121 and 5/89 foetuses with malformations). It is considered noteworthy that one foetus at 15 mg/kg, and two foetuses at 25 mg/kg - all from different mothers - manifested kidney and ureter malformations. Overall, the embryofoetal/offspring NOAEL for the rabbit FEED study is set at <5 mg/kg (LOAEL 5 mg/kg, as opposed to the applicants suggestion of 15 mg/kg).

PPND: In the rat PPND study (5, 15 & 25 mg/kg, maternal oral exposure between GD6 and PND21) generated adverse clinical signs, reduced bodyweight, enlarged spleen in some animals, plus a reduction in effective pregnancies at 25 mg/kg. There was also a minimal to slight growth inhibition in F1 pups from birth throughout lactation (pup body weight -10% to -14%) followed by reduced food-intake also some additional days post-weaning (up to PND42 to PND56). The NOAEL for both mothers and offspring is set at 15 mg/kg.

4.5.6. Toxicokinetics and exposure margins

The AUC parameter was considered the most relevant considering the oral exposure route. Based on animal species-specific popPK models using single dose and 13w repeat-dose toxicokinetics (TK) data (see below), cumulative AUC values were used for animal-to-human exposure margin estimates. With regard to drug metabolism, several animal studies also measured the levels of the SCYX-3109 metabolite which is considered a minor metabolite (less than <1% in human and <5% in animal models of the total exposure) and there are also no indications of any particular toxicological functionality. Acoziborole exposure generally increased in a dose proportional manner at the range of doses tested in repeated dose toxicity studies in rats, in a less than dose proportional manner in dogs and in a more than dose proportional manner in rabbits.

The NOAEL for rats in the 28d and 13w repeat-dose toxicity study was set at 5 mg/kg. At this dose the corresponding acoziborole exposures were as follows:

- At d28; Cmax (M/F) 595/7960 ng/mL and for AUC0-last (M/F):135850/165180 ng x h/mL (cumulative AUC: 3808/4620 µg x h/mL). The Tmax was 2h-24h (mostly 4h-8h) at d1 and 4h-8h at d28 in the 28d+28d rat study.
- At d91 Cmax (M/F) 5890/6610 ng/mL and for AUC0-24h (M/F) 104850 /119740 ng x h/mL (cumulative AUC 8421/9422 µg x h/mL). The d1 to d91 Tmax was 2-8h.

For dogs, the 14d-to-28d study NOAEL was set to 5 mg/kg (actually <NOAEL as LOAEL was 5 mg/kg) and the NOAEL for the 13w study was 20 mg/kg.

- At d28; Cmax (M/F) 17050/36980 ng/mL and for AUC0-24h (M/F) 374860/640570 ng x h/mL (cumulative AUC 10500/17948 µg x h/mL). The Tmax was 2h at 5 mg/kg and 6h-18.67h at 15 and 40 mg/kg.
- At d91; Cmax (M/F) 31267/17700 ng/mL and for AUC0-24h (M/F) 644751/368497 ng x h/mL (cumulative AUC 52093/37229 µg x h/mL). The Tmax was 2h-24h at d1 and d91 across doses and sex.

Regarding DART, no TK measurements were made for the rat FEED study and the cumulative AUC at the reproductive NOAEL of 25 mg/kg (♂ 17175 & ♀ 32100 µg x h/mL) was based on general toxicity studies in rat and is therefore an estimate with greater uncertainty. For the EFD studies, the rat maternal and embryofoetal NOAEL was 15 mg/kg whereas the rabbit maternal and embryofoetal

NOAEL is set at <5 mg/kg.

- At Gd17 in rat; Cmax (F) 19900 ng/mL and AUC0-24h (F) 378000 ng x h/mL (cumulative AUC 4536 µg x h/mL). The Tmax was 4h-8h across days and doses.
- At Gd19 in rabbit; Cmax (F) 27700 ng/mL and AUC0-24h (F) 250000 ng x h/mL (cumulative AUC for 5 mg/kg not calculated, see Discussion). The Tmax (non-pivotal and pivotal rabbit studies) was mostly in a range up to 24h except in the pivotal study where the range was up to 96h (15 mg/kg) and 192h (after 25 mg/kg).

It can be noted that for both rat and rabbit, the parent compound manifested greater than dose proportional increase at 15 mg/kg/d and 25 mg/kg/d although this was most evident for the SCYX-3109 metabolite. The metabolite also demonstrated >2 dose accumulation although it is unclear if this has any bearing on the toxicity seen. In the rat PPND study, the maternal and offspring NOAEL was 15 mg/kg.

- At PND21; the maternal Cmax (F) 11300 ng/mL and AUC0-last (F) 507000 ng x h/mL. The Tmax was 1h-4h. The lactation dependent offspring/pup (F1) PND21 average plasma concentration was 2650 ng/mL (decreasing from 7480 ng/mL on PND4). The calculated cumulative AUC – based on extrapolated data from general toxicity rat studies – was 19 315 µg x h/mL.

Exposure margins

The applicant has provided a cumulative animal AUC based on popPK models developed in rats and dogs and dosing regimens used in the 13-week studies, and DART studies. The animal-to-human exposure margins were based on a human AUC of 6440 µg x h/mL (in plasma, based on a blood-plasma-ratio of 0.81x, and corresponding to a human dose of 960 mg). For the fertility (FEED) study, the cumulative exposure for the 23 days once daily (OD) treatment regimen was calculated using the cumulative exposure estimated for the 43 days OD treatment regimen adjusted by the number of days of treatment (i.e. multiplied by 23/43). For the other studies, the AUC0-24h values calculated during the last day of study treatment were multiplied by the number of days of treatment to obtain a rough estimation of the cumulative exposure.

Study ID / species	NOAEL (mg/kg)	Animal AUC (µg x h/mL)	Cumulative animal AUC	Animal-to-human Exposure Multiple	
(RDT: Repeat-dose toxicity)		♂ / ♀	♂ / ♀	♂	♀
Rat 28d RDT +28d recovery	5	136 / 165	3808 / 4620	0.6x	0.7x
Rat 13w RDT +6w recovery	5	105 / 120	8421 / 9422	1.3x	1.5x
Dog 14d-to-28d RDT +42d recovery*	5	375 / 641	10500 / 17948	1.6x	2.8x
Dog 13w RDT +6w recovery**	20	645 / 368	52093 / 37229	8.1x	5.8x
Rat FEED study***	Reproductive 25	--	17175 / 32100	2.7x	5.0x

	Maternal 5	--	Not calculated	--	--
Rat EFD study	Offspring 15	-- / 378	-- / 4536	.--	0.7x
Rabbit EFD study****	Offspring 15	-- / 250	-- / 3500	--	0.5x
	Offspring <5	-- / 36.6	-- / 512	--	0.1x
Rat PPND study	Offspring 15	--	Pups: 19 315	3.0x	3.0x

* The NOAEL of 5 mg/kg in the 14d-to-28d dog study is considered a LOAEL by the rapporteur as the same but weaker effects are seen as those that are more obvious at the mid dose (15 mg/kg). But this gives no changes in the margin exposure estimates as there is no lower dose with TK-data.

** There are some signs of male reproductive organ toxicity in 13w+6w dogs which, although not fully conclusive, can also not simply be dismissed as they are similar to those seen in the rat studies.

*** The rat FEED study did not contain TK-data. The cumulative animal AUC was predicted as described above in the beginning of this section. Exposure margins were estimated for the max dose of 25 mg/kg (no reproductive effects) which is above the general study NOAEL of 5 mg/kg.

**** The applicants embryofetal NOAEL (offspring NOAEL) was initially set at 15 mg/kg which was not supported by the rapporteur. A NOAEL < 5 mg/kg and a LOAEL of 5 mg/kg is considered more reasonable.

4.5.7. Local tolerance

No local tolerance studies were conducted as acoziborole was indicated for single oral administration in humans.

4.5.8. Other toxicity studies

Dependence

No dedicated dependence studies have been performed for acoziborole. The applicant has conducted a theoretical drug abuse liability assessment (DALA) for acoziborole (see Discussion below) as it was shown to cross the blood brain barrier (BBB) and be present in cerebro-spinal fluid.

Metabolites

In human, the metabolism of acoziborole was limited and slow. Acoziborole represented almost the totality of the plasma radioactivity (95%). None of the metabolites represented more than 10% of the total circulating plasma radioactivity in human. One of the human minor metabolites identified (SCYX-3109) is derived from oxidative deboronation of acoziborole. No dedicated toxicological SCYX-3109 metabolite studies have been conducted beyond toxicokinetic measurements in some of the animal studies.

Phototoxicity

Acoziborole has a molar extinction coefficient (MEC) of 3470 L mol^{-1} cm^{-1} at 290 nm which is above that trigger value of 1000 L mol^{-1} cm^{-1} but is below 1000 L mol^{-1} cm^{-1} at 310 nm. An 3T3 Neutral Red Uptake Assay (concentration range 0.0316 to 100 µg/mL, chlorpromazine as positive control) did not find any signs of cytotoxicity or phototoxicity .

Impurities

A number of pharmaceutical impurities have been identified. Based on ICH M7 classification, and besides to nitrosamine impurities, based on in-silico assessment (DEREK, Leadscope) this included four class II and 18 class III impurities. Among the class II impurities, the SCYX-5144 and SCYX-8624 impurities - which are intermediates in the synthesis of acoziborole - were assessed in an Ames test and established to be mutagenic. Two nitrosamine impurities (N-nitrosodimethylamine or NDMA and Dinitrosodimethylethylenediamine or NDMEA) have also been identified. NDMA is an established genotoxic carcinogen (lifetime acceptable daily intake at 96 ng/d) whereas NDMEA is not characterised empirically - although in-silico analysis of the chemical structure would indicate that NDMEA is roughly similar in mutagenic potency (see the Quality section for additional details).

4.5.9. Ecotoxicity/environmental risk assessment

The applicant has decided not to conduct an ERA as the product is presently intended only for regions outside the EU (see Discussion). As such, no conclusion can be made about environmental risk.

4.6. Overall discussion and conclusions on non-clinical aspects

4.6.1. Discussion

Pharmacology

Primary pharmacodynamics is not covered by the the non-clincial section. Aspects of safety pharmacology are incorporated in the toxicology discussion.

That being said, shortly, acoziborole (also SCYX-7158, AN5568) is a 3,3-dimethyloxaborole-6-carboxamide derivative of the benzoxaborole class, developed as an oral treatment for human African trypanosomiasis (HAT). Its pharmacological effect is mediated by inhibition of CPSF3, a parasite-specific endonuclease responsible for pre-mRNA processing. The boron atom within the oxaborole scaffold is essential for activity, forming interactions with the CPSF3 active site to block parasite mRNA maturation without affecting the host enzyme, ultimately leading to parasite death.

Regarding secondary pharmacology, off-target activity of acoziborole was evaluated in vitro across a panel of receptors, ion channels, transporters, and enzymes. No significant interactions were observed at concentrations up to 10 µM. Cytotoxicity assays in L929 fibroblasts showed no measurable effect on cell proliferation up to 50 µg/mL.

Pharmacokinetics

Based on the nonclinical data, acoziborole demonstrates a pharmacokinetic profile characterized by slow absorption, wide tissue distribution, high plasma protein binding, minimal metabolism, and predominant faecal elimination. Acoziborole show passage over the blood brain barrier when unbound to plasma proteins. Analytical methods for analysis of acoziborole (and minor metabolite M9) in plasma samples from rats, rabbits, and dogs have been submitted and made available. They have been found

to be adequate for their intended purpose and have been sufficiently validated. When relevant, compliance with GLP has been ensured.

Absorption of acoziborole is strongly influenced by formulation and solubility, with systemic exposure generally increasing with dose. In nonclinical species, oral absorption was moderately rapid in rodents, slower in monkeys, and markedly prolonged in dogs, reflecting species-specific differences in gastrointestinal transit and dissolution. While solubility-limiting factors impacted the rate of absorption, overall bioavailability was moderate to high across species, and inter-individual variability in humans appears low, supporting predictable systemic exposure. In humans, absorption is extremely slow, but bioavailability appears high, and interindividual variability is relatively low, supporting acceptable predictability of plasma concentrations and the feasibility of standardized dosing.

No dedicated PK studies were conducted in rabbits (used in DART studies). The lack of full PK characterization in rabbits introduces some uncertainty but given high protein binding and minimal metabolism in other species, along with available AUC/Cmax from TK studies, the likelihood of this lack of PK knowledge to impact the assessment of systemic exposure or reproductive toxicity is considered low. Furthermore, the exposure margins are low/none to humans and further PK evaluations in rabbits would not dramatically affect the conclusions drawn in reproductive studies (see toxicology section).

Distribution studies demonstrate that acoziborole is widely distributed to tissues, particularly liver, thyroid, kidney, and subcutaneous fat. CNS exposure occurs at levels consistent with the free fraction in plasma, indicating that the drug can reach target organs such as the brain. High plasma protein binding across species suggests a low free fraction, which may contribute to both distribution patterns and prolonged systemic persistence. Placental transfer and milk excretion have been shown in rats, confirming the capacity of the compound to cross biological barriers, although the implications for humans are mitigated by the low free fraction. No evidence of melanin binding was observed. Tissue half-lives were prolonged, particularly in female rats, but sex differences do not appear to constitute a significant risk to humans. Human data show that the apparent volume of distribution is 109 L and CNS exposure can be predicted from the free plasma fraction, supporting the translational relevance of nonclinical tissue distribution data.

The metabolism of acoziborole is limited across species. In vitro studies with liver fractions of S9, microsomes and primary hepatocytes demonstrate high metabolic stability, with half-lives exceeding 350 minutes and low intrinsic clearance. The primary metabolic pathway involves oxidative de-boration followed by glucuronidation to form M9 and M4, which were consistently observed in mouse, rat, dog and monkey hepatocytes. In vivo study on the present metabolites was conducted only in rats, which confirms sufficient concordance with the in vitro findings. In humans, no major metabolite has been observed, and the parent compound represents >95% of the circulating material, confirming that metabolism is limited and that the nonclinical metabolic pattern is broadly predictive of human exposure.

Excretion occurs predominantly via feces, with minor renal elimination in rats. Half-lives vary between species but generally increasing with animal size (t ½ = mice < rats < dogs). In humans, the apparent half-life is extremely long (~296 hours), consistent with non clinical finings data suggesting low clearance, leading to its elimination through hepatobiliary excretion, which is limited by its slow metabolism. Furthermore, data in dogs do provide indication of enterohepatic recirculation (multiple plasma peaks and that charcoal effectively reduced elimination time). Paradoxically, there were indications that the acoziborole was not detected in dog bile after 48 hours; however, the absence of detectable drug in bile may be attributable to its slow absorption, suggesting that it had not yet reached the bile thus not contradict hepatobilary excreation.

Overall, the nonclinical pharmacokinetic profile of acoziborole indicates slow, solubility-limited absorption, high plasma protein binding, broad tissue distribution, CNS penetration corresponding to

the free plasma fraction, minimal metabolism, and primarily faecal elimination. Although species-specific differences in absorption and accumulation were observed, the data support a predictable systemic exposure in humans. No major human metabolites were identified, and the nonclinical models used are considered appropriate to predict human pharmacokinetics.

Toxicology

Animal models

The toxicological animal models (rat, dog & rabbit) all had similar metabolic capacity in that they generated the SCYX-3109 metabolite, supporting the relevance as animal models for humans (<1% of total exposure in humans, 1-2% in animals). That being said, the overall metabolite profile (besides the SCYX-3109 metabolite) for rabbit was not characterised in the non-clinical pharmacokinetics section, leaving some uncertainty. The animal models do not reach the long elimination half-life seen in humans (see Clinical section), indicating that there are some species differences regarding rate of absorption, elimination and/or enterohepatic circulation. In humans, the terminal half-life was up to ~13d. In the animal studies, the acoziborole terminal half-life was shorter and ranged from 31 to 50h in rat, and 35 to 83.1h in dog. That being said, based on systemic exposure, non-clinical popPK models for repeat-dose exposures in rat and dog indicate that human exposure (based on single 960 mg dose) during the first 1-2w is roughly represented by the lower doses (5 to 20 mg/kg) used in the animal studies – followed by a time period where the non-clinical systemic exposure is greater than that estimated in humans.

General toxicity

Radio-labelled distribution studies in rat (see also the non-clinical Pharmacokinetics section) indicate that acoziborole is widely distributed to tissues, with the highest exposure observed in the liver, thyroid, kidney and subcutaneous fat. Based on the toxicity tests, acoziborole had several target organs that were shared between rats and dogs at low (mostly <5x) animal-to-human margins: intestines (duodenum, jejunum, ileum, colon), liver, pancreas, adrenal glands, spleen, thymus, testes and epididymides. Rats manifested more extensive male reproductive organ toxicity and there were also some signs of such effects in dogs. Both animal models manifested a reduction in red blood cells (RBC), haemoglobin and hematocrit and in some studies increase in reticulocytes – indicating exposure induced anaemic conditions. Rats (and rabbits) died at higher doses – possibly due to digestive system/gastrointestinal toxicity lesions. In animals without unscheduled deaths, most effects were fully or partial reversible. The 13w+6w dog study (5 to 20 mg/kg) manifested much less toxicity than the 14d-to-28d+42d dog study (5 to 40 mg/kg, 14d high-dose exposure, 28d low- and mid-dose exposure) but this is likely due to that former study had a lower maximum dose and also shifted to every second day exposure after ~4 weeks. Overall, with regard to adverse clinical signs and reduced body weight & food-intake, the data indicates that rats, in sub-chronic exposure settings, begin to be sensitive at 30 to 40 mg/kg whereas dogs have a range of 15 to 20 mg/kg. Generally, these effects were partially or fully reversible.

Cardiotoxicity notes: While there are signs that acoziborole can act as a weak hERG inhibitor, neither in-vivo safety pharmacology (maximum dose 40 mg/kg) or general toxicity studies in dog (maximum doses 20 to 40 mg/kg) – which investigated cardiophysiological endpoints – detected any exposure induced changes. It can be noted that based on popPK models using TK data from single dose and up 13w repeat-dose exposures in dog (dose-range 5 to 20 mg/kg) the human exposure i slightly higher than animal systemic exposure (from a single 960 mg dose) during roughly the first week. For the 13w dog study, this leaves some uncertainty regarding potential cardiotoxicity driven by high initial systemic exposure levels. But as the safety pharmacology dose-escalation study reached 40 mg/kg, it is considered likely that one has reached concentrations higher than human exposure and thereby covered any possible Cmax-driven cardiotoxicity. So overall, while clinical studies have founds signs of

shortened QT intervals, and besides the in-vitro hERG study, there are no corresponding non-clinical findings (in dog) that can help explain or interpret the clinical findings.

DART

With regard to reproductive organ toxicity and the FEED study, the 28d+28d rat study generated (especially male) reproductive organ toxicity at ≥40 mg/kg (with histopathological effects evident at doses lower than those that caused organ weight changes). In the rat FEED study, no histopathological assessment was conducted on the paternal reproductive organs (e.g, testes, epididymides) which can be considered a weakness. As such, while there was no impact on the primary endpoint of interest for the FEED study (fertility, early embryogenesis), there is some degree of uncertainty regarding the state of the paternal reproductive organs in the FEED study.

In the embryofoetal developmental (EFD)/teratogenicity studies, acoziborole was found to cross the placenta and to be excreted in milk of rats. The EFD studies demonstrated that rats are less sensitive to acoziborole exposure than rabbits.

For the rabbit EFD study (at 5, 15 and 25 mg/kg, between GD6 to GD19, termination on GD29), the embryofoetal NOAEL is <5 mg/kg due to an increase in resorptions and post-implantation loss seen at 5 mg/kg. Regarding malformations, there were more malformations at 25 mg/kg with a possible trend of increase at 15 mg/kg there was also one foetus at 15 mg/kg, and two foetuses at 25 mg/kg - all from different mothers – that shared kidney and ureter malformations. The animal-to-human exposure margins for the EFD outcomes are <1x (0.7x in rats and < 0.1x in rabbits). As such, there are no safe exposure margins between rabbit and human systemic exposure.

In the rat PPND study, there was pup exposure via lactation (until weaning PND21) and also some reduced developmental growth (during the lactation period and also spanning some days post-weaning) of the pups at the maximum dose of 25 mg/kg. This has also been described in the SmPC 4.6 and 5.3. It can be noted that the TK data in pups shows that the exposure levels in the offspring decrease between PND4 and PND21. An exposure margin of 3x has been calculated but it is unclear how precise or representative that estimate is for human exposure. That being said, the prediction still indicates that the exposure margin to humans in likely low. The PPND results are noted in the proposed SmPC which is supported.

No dedicated juvenile toxicity study has been conducted. The applicant argues that there are no signs in the other existing toxicity studies that would indicate a particular juvenile toxicity hazard. While there were no clear adverse signs in those organ systems commonly associated with postnatal & juvenile development, considering the many organ systems affected in the 1w to 4w exposure studies in rat and dog, and the minor growth retardation in the rat PPND study, there remains some degree of uncertainty regarding to what extent an juvenile toxicity profile would be similar or different from the observed general toxicity profile.

Toxicokinetics & animal-to-human exposure margins

As noted above regarding animal models, there are some differences between humans – with a long terminal half-life - and the toxicological animal models (especially regarding the elimination half-life and there is also some uncertainty to what extent there are differences for rate of absorption and extent of enterohepatic circulation). In order to compare the repeat-dose animal data to the human single dose setup, animal species-specific popPK models (incorporating single and repeated doses) were used to calculate cumulative AUCs for the purpose of animal-to-human exposure margin estimates. Overall, the clinical exposure margins were low (<10x, mostly <5x) or absent (<1x, including for EFD).

Immunotoxicity

No dedicated immunotoxicity studies have been performed. There were signs at higher doses in the general toxicity tests (in rats at high dose levels of 80, 140 or 400 mg/kg/day and in dogs at ≥15 mg/kg in the 14d-to-28d+42d study) of lymphoid depletion and or white blood cell count reductions. Acoziborole had also an impact on the adrenal glands (cortical hypertrophy, vacuolisation) at low doses (≥5 mg/kg) in both rats and dogs. The non-clinical and clinical relevance of the observed adrenal changes is unclear but may possibly be of immunological interest as this organ is relevant for bodies mounting an immunological response.

Drug dependence

Based on the ncPK studies, brain and/or CSF distribution of acoziborole was shown in mice, rats and monkeys. A theoretical drug abuse liability assessment (DALA) argues that the acoziborole is highly ON-target specific and that there should be no or little risk for neurotoxicity. While the Secondary pharmacology screening for off-targets would support this view, the extensive range of toxicological effects seen in rats and dogs and rabbits would indicate that acoziborole is less than 'clean' and that off-targets may exist in mammals. That being said, there are no clear signs of CNS effects in the animal studies and it is agreed that there no non-clinical (or clinical) signs that would require this aspect to be explored further.

Phototoxicity

Acoziborole has a MEC of 3470 L mol^{-1} cm^{-1} at 290 to 300 nm (above that trigger value of 1000 L mol^{-1} cm^{-1}). An 3T3 Neutral Red Uptake Assay (GLP) of acoziborole did not find any indications of phototoxicity. It can be noted that the non-clinical PK studies do not indicate any particular pigment binding properties and there have been no clear clinical signs of phototoxicity.

Environmental risk assessment

The present medicinal product was assessed via an EU-M4all application which can but, depending on intended regions of usage, is not required to include an environmental risk assessment (ERA) by analogy to the EU standards for marketing authorisation applications. The MAH did not conduct an ERA as the product is intended for regions outside the EU. This is acceptable, but this also means that any future extension to the EU will require the submission of an ERA in line with the, at the time, active CHMP ERA guideline. As such, there exists presently no assessment and conclusion regarding the environmental risk of acoziborole.

4.6.2. Conclusions

There are no objections from a non-clinical perspective.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

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

The Applicant described in the dossier the mechanisms in place for study monitoring, to ensure the quality of study conduct and to check the accuracy and validity of data. Details of four types of visit were provided (site evaluation in new centres, initiation, routine monitoring, close-out visit). Monitoring was more intensive for the first 20 patients included in the study (100% source data verification [SDV]), then a mix of complete and partial SDV was conducted (100% SDV of selected criteria for all patients and 100% SDV every 5 patients). The Applicant has taken reasonable steps to ensure data integrity, in accordance with national legislation on data protection. The data management system had an audit trail to log every change made to the database.

Patients did not receive any payment to participate in the study; however, they were reimbursed for their travel costs and any essential medication required during the study and received food free of charge for the duration of hospitalisation for study purposes and follow-up visits. To ensure that participation in the study was voluntary, all patients diagnosed with human African trypanosomiasis (HAT) during the screening period were treated at the hospital/investigational centre in accordance with current guidelines for treating HAT, even if they were not included in the study in the end (due to ineligibility or because they did not wish to participate). If treatment required hospitalisation, food was provided to the patient during this period in the same way as for study participants.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Table 4: Tabular overview of main clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
DNDi-OXA-02-HAT (DRC, Guinea)	Completed	Efficacy & safety SA, OL Historical external control	Single PO dose acoziborole 960 mg (3 x 320 mg)	208 patients ≥15 yrs old with T+ g-HAT
DNDi-OXA-04-HAT (DRC, Guinea)	Completed	Safety DB, PC	Single PO dose acoziborole 960 mg (3 x 320 mg)	Patients ≥15 ys old with Tnc g-HAT

R = randomised; DB = double blind; PC = placebo controlled; SA = single arm; OL =open label; yrs = years; PO =oral; T+ = serologically and parasitologically-confirmed *T. b.* infection; Tnc = serologically but parasitologically-**not** confirmed *T. b.* infection;

5.2. Clinical pharmacology

5.2.1. Methods

Acoziborole and the metabolite SCYX-3109 were quantified in plasma with validated bioanalytical methods using LC-MS/MS assay with protein precipitation, with an LLOQ of 25.0 ng/mL for acoziborole

and 10.0 ng/mL for SCYX-3109. In Phase II/III studies, acoziborole was quantified in DBS and dried CSF with validated LC-MS/MS assay methods with an LLOQ of 25.0 ng/mL.

A comparative study was performed to analyze the concentrations of acoziborole measured in plasma or DBS samples using the same 4 QC concentrations. The blood-to-plasma ratio was between 0.83-0.86, in line with the blood-to-plasma ratio of about 0.8 reported from in vitro studies.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Acoziborole is an antiprotozoal drug indicated for adolescent and adults seropositive for g-HAT. The proposed dose is a single administration of 960 mg (three 320 mg tablets). At the clinical dose, absorption is slow with a time to maximum plasma concentration (tmax) in the range of 48-96 hours in healthy sub-Saharan Africans. Also the elimination was slow, with a half-life of 267-411 hours for different doses in healthy sub-Saharan Africans and 296 hours (approximately 12 days) in the target population administrated 960 mg as a single dose. Acoziborole is a strong inducer of CYP3A4 and several other enzymes and also a strong CYP2D6 inhibitor. Considering the terminal half-life of acoziborole, the effects on enzymes may persist for 3 months.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

The objective was to build a popPK model for acoziborole after single oral dose in fasting condition in patient with g-HAT at different stages, in order to determine population PK parameters.

All g-HAT patients (19.7% at early or intermediate stage and 80.3% at late stage.) from study DNDi-OXA-02-HAT were included in the analysis dataset. A total of 1508 acoziborole concentrations (dry blood spot (DBS) samples) from 208 patients were analysed for the PopPK analysis. Samples up until 240 hours after dose are shown in Figure 1 (and additional samples collected up to 6 months after dosing).

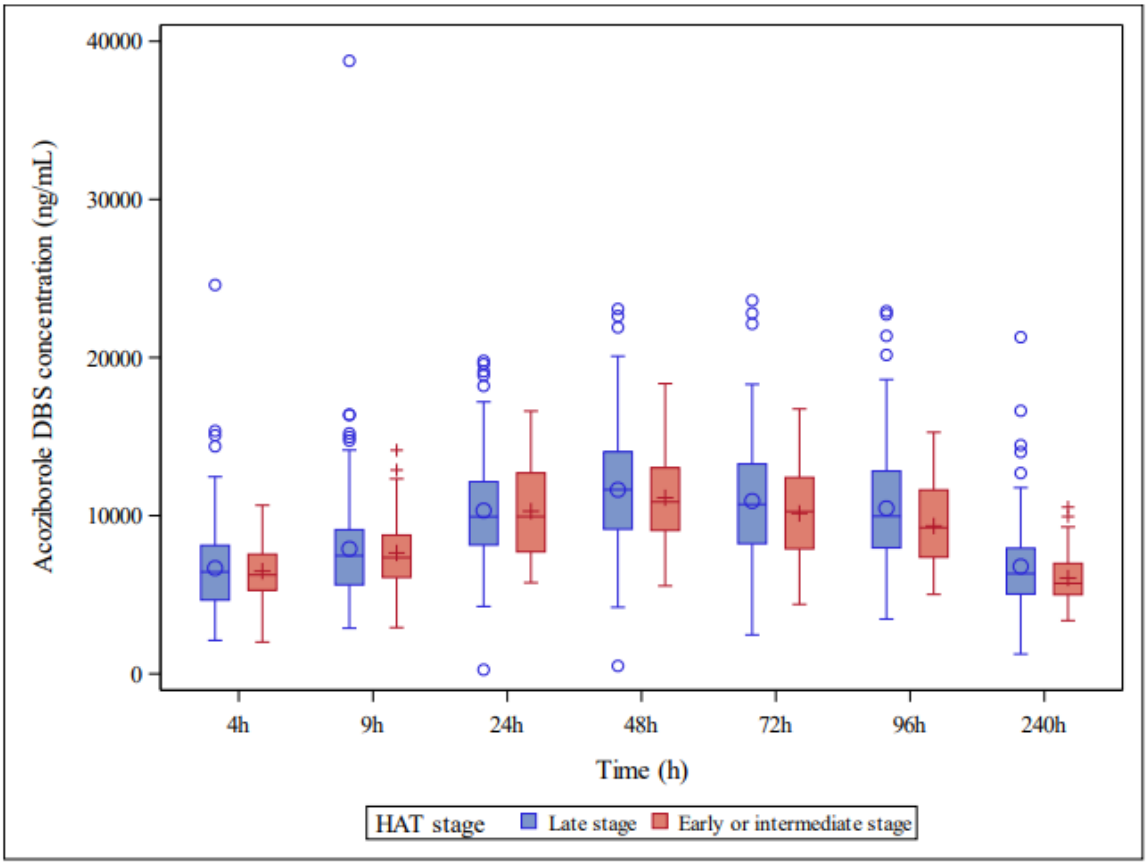


Figure 2. Distribution of Acoziborole (ng/mL) DBS concentration by HAT stage.

A total of 208 subjects (56.3% male and 43.7% female) were included in the analysis. The mean age was 34 years, ranging between 15 and 68 years, weighing between 30.9 – 88.9 kg with mean 53.19 kg.

The population PK analysis was performed using non-linear mixed effect model (NLME) in NONMEM (Version 7.5). Different models were explored such as one- and two-compartment disposition models and zero or first order absorption with or without lag time. Model evaluation and selection was based on the improvement in the objective function and the pattern in the residual plots.

The covariates explored during the covariate model development included body weight, age, AST, ALT, ALP, total bilirubin, total protein, albumin, disease stage and concomitant medications (rifampicin and carmazepine). The covariates were explored using a stepwise procedure including a univariate analyses followed by backward elimination. Statistically significant covariates were subsequently assessed for clinical relevance using forest plots.

A one-compartment model with a sequential mixture of first-order absorption followed by a zero-order absorption and linear elimination was found to best describe the data. The only included covariate was body weight on clearance and volume, including fixed allometric exponents (1 for volume and 0.75 for clearance).

Table 5. Acoziborole popPK Base model parameters estimates

	Estimate (%RSE)	95% CI	Variability	Shrinkage
CL/F (L/h)=$\theta 1*(Weight/70)^{0.75}*EXP(\eta_1)$				
q_1: CL/F typical value	0.24 (3.76%)	(0.222; 0.257)		
h_1: (IIV CL/F)	0.112 (20.1%)	(0.068; 0.156)	CV= 33.5%	6.14%
V_2/F (L)=$q_2*(Weight/70)*EXP(h_2)$				
q_2: V_2/F typical value	109 (2.44%)	(104; 114)		
Cov (CL/F,V_2/F)	0.09 (16.2%)	(0.061; 0.118)	R= 0.833	
h_2: (IIV V_2/F)	0.103 (14.7%)	(0.073; 0.133)	CV= 32.1%	3.87%
k_a (h^{-1})=$q_3*EXP(h_3)$				
q_3: k_a typical value	0.289 (7.83%)	(0.244; 0.333)		
h_3: (IIV k_a)	0.291 (13.4%)	(0.214; 0.367)	CV= 53.9%	22.24%
D_1 (h)=$q_4*EXP(h_4)$				
q_4: D_1 typical value	25.8 (8.59%)	(21.5; 30.2)		
h_4: (IIV D_1)	0 (FIX)			
t_{lag} (h)=$q_5*EXP(h_5)$				
q_5: lag time typical value	9.67 (0.09%)	(9.65; 9.69)		
h_5: (IIV t_{lag})	0 (FIX)			
F_1=$q_6*EXP(h_6)/(1+ EXP(h_6))$				
q_6: F_1 typical value	0.747 (4.28%)	(0.684; 0.810)		
h_6: (IIV F_1)	0 (FIX)			
Residual error				
e_1: proportional component	0.031 (18.3%)	(0.020; 0.042)	CV= 17.7%	
e_2: additive component	242 (48%)	(14.4; 470)	SD= 15.5 ng/mL	
Run=R017a: Objective function = 23845.805/ AIC= 23875.8 - Condition number: 195.259				
RSE: Relative standard error; CI: Confidence interval; CV: Coefficient of variation				

A VPC of the final model is included in Figure 3.

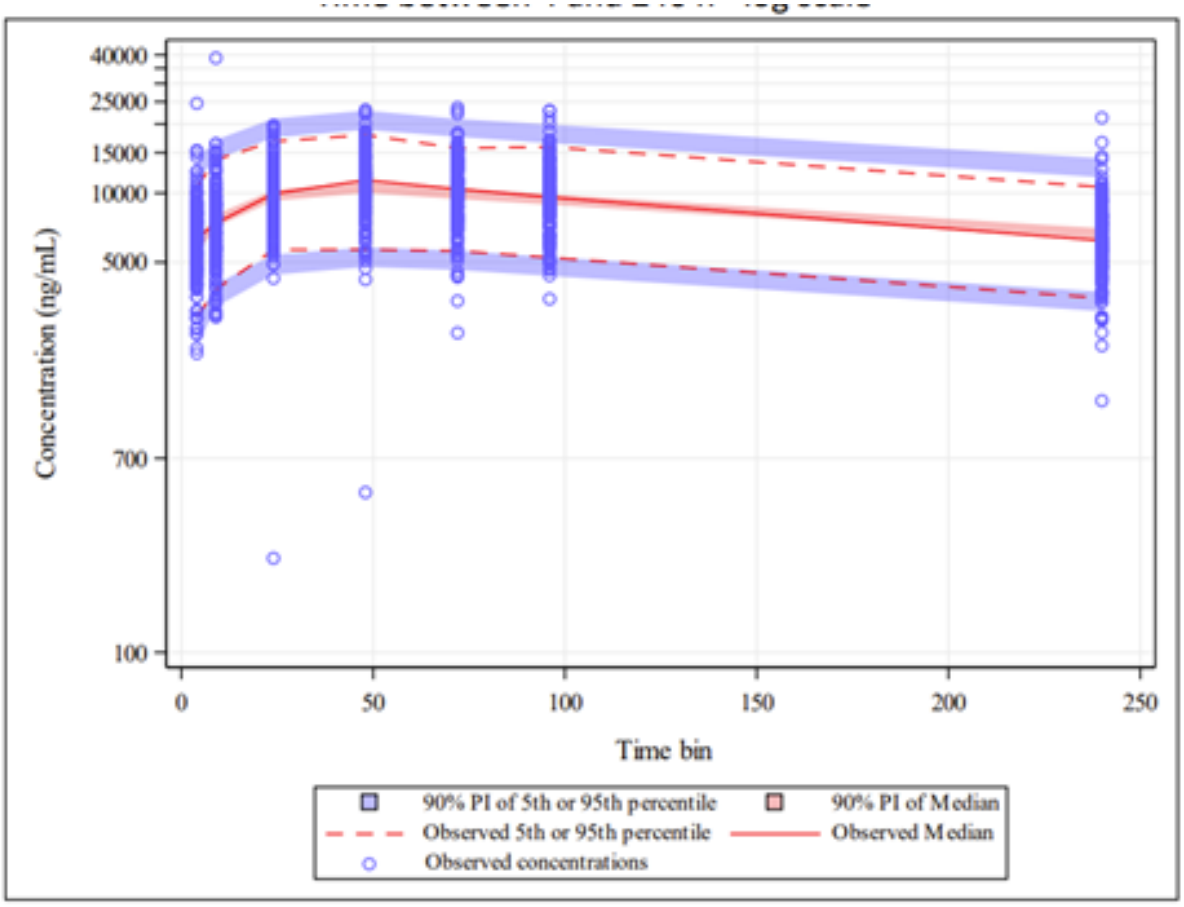


Figure 3. VPC for acoziborole concentration as a function of time in HAT patients.

5.2.2.2.2. Physiology based pharmacokinetic model

PBPK model to predict DDI

The Applicant submitted a PBPK model to evaluate the acoziborole drug-drug interaction (DDI) potential as a CYP3A4 inducer and a CYP2D6 time-dependent inhibitor (TDI). The model was used to predict the duration of the DDI-effect of acoziborole on CYP2D6 and CYP3A4 probe substrates and prospective co-administered drug substrates to guide drug labelling. Clinical DDI data on the interaction with sensitive CYP3A4 and CYP2D6 probe substrates are available. The model predicted that the interaction between midazolam and acoziborole will be moderate (AUC or Cmax GMR 2 - 5) up to 9 weeks after acoziborole, transitioning to a weak interaction up to 15 weeks. For CYP2D6 (TDI), a moderate interaction between dextromethorphan and acoziborole was predicted up to 18 weeks post acoziborole dose by the model.

Additionally, the model was used to predicted outcomes of DDI with acoziborole as a perpetrator for sensitive substrates of CYP1A2 (caffeine), CYP2B6 (bupropion), CYP2C8 (rosiglitazone and repaglinide), CYP2C9 (S-warfarin), CYP2C19 (omeprazole), and breast cancer resistance protein (BCRP) (rosuvastatin). No clinical DDI data were available to verify the model prediction for these enzymes.

5.2.2.3. Absorption

Acoziborole drug substance is practically insoluble in aqueous media at pH 1.2, 4.5 and 6.8, and the single therapeutic dose of 960 mg cannot be dissolved in the volume of 250 mL at any pH. In all

simulated biological tested media acoziborole is found to be a poorly soluble compound with a maximum solubility of 0.13 mg/mL observed in the Fed State Simulated Intestinal Fluid (FeSSIF).

In vitro studies indicate high permeability of acoziborole. No human data from intravenously administrated acoziborole is available and thus absolute bioavailability is unknown. The absorption of acoziborole was estimated to approximately 70%, as most of the radioactivity was excreted in faeces >72 hours after administration in the mass balance study (based on the assumption that the absorption phase has been covered by 72 hours as the average total time for food to pass through the digestive system is about 24 to 72 hours).

In the BCS-system high permeability can be concluded when the absolute bioavailability is ≥85% or alternative methods outlined in the ICH M9 guideline. For acoziborole these requirements are not fulfilled and therefore it is classified as a BCS-class IV substance.

In vtiro acoziborole is a substrate of P-gp but not of BCRP or OATP1B1/1B3.

In the first-in-human study in healthy male adults of sub-Saharan African origin Acoziborole appeared rapidly in plasma (1 hour post-dose). Its absorption was slow and prolonged, with a tmax reached around 72 hours (range from 48 to 96 hours) after a single oral administration of 960 mg and concentrations remaining quite stable until 96 hours post-dose after which the plasma concentration started to decrease very slowly (see . Mean Acoziborole Cmax was 19.6±4.16 µg/mL.

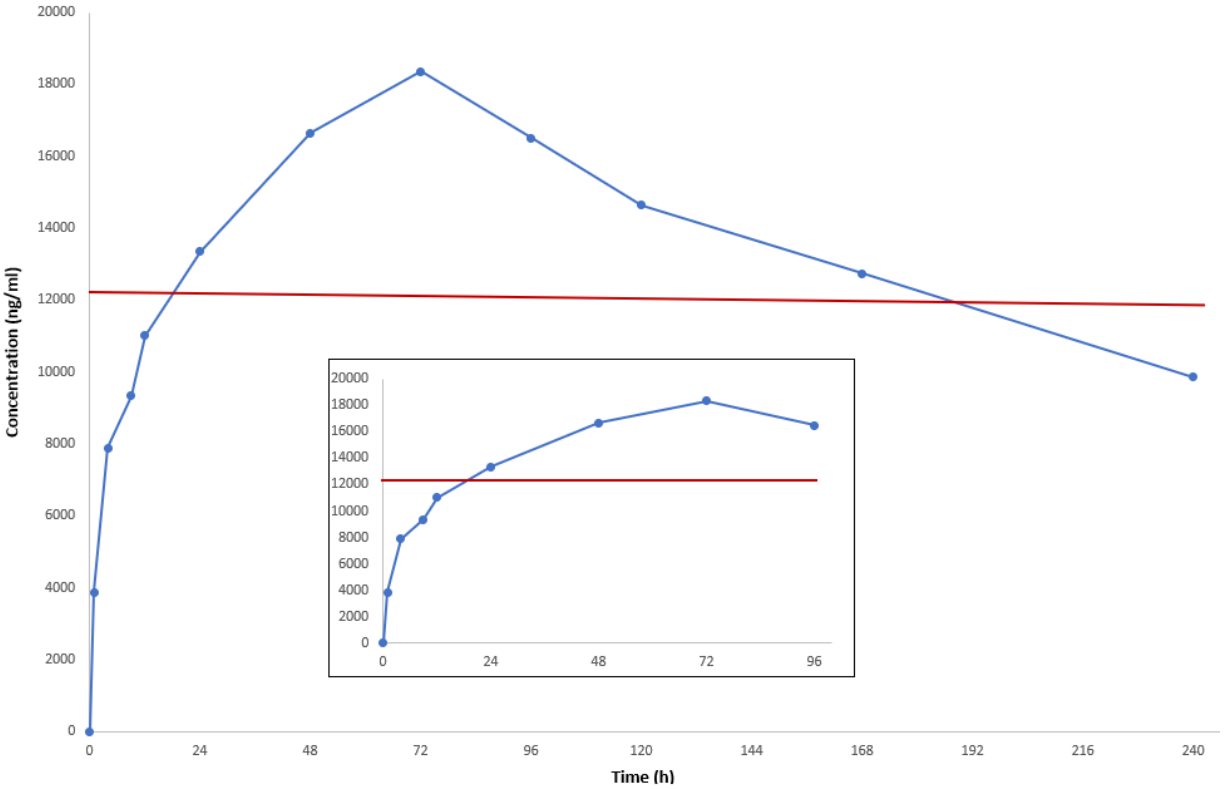


Figure 4. Mean plasma concentration time profile for 960 mg administered as a single dose to 6 healthy individuals of sub-Saharan African origin (study DNDiOXA001). No concomitant activated charcoal was administered. Red line indicates the targeted plasma concentration. The inset shows the profile for the first 96 hours.

At least for lower doses there were multiple peaks observed in acoziborole plasma concentration profiles at early time points suggesting entero-hepatic recycling. Co-administration with activated

charcoal in the elimination phase (96 hours post-dose) was evaluated but overall activated charcoal had a minor effect on acoziborole clearance.

Influence of food

No clinical study was conducted to investigate the effect of food on acoziborole bioavailability. In all the clinical studies, a single oral dose of acoziborole was administered under fasting conditions in the morning. The SmPC recommends to take acoziborole without food applying similar restrictions as those used in the conducted patient studies.

5.2.2.4. Bioequivalence

Different formulations have been used in the clinical studies. The relative bioavailability of acoziborole administered as a tablet versus capsule formulation was investigated in the Phase I clinical study DNDiOXA001. A crossover study could not be conducted due to the long $t_{1/2}$ of acoziborole. Therefore, the relative bioavailability of the tablet versus capsule was assessed by comparing the exposure of acoziborole over 96 hours in participants of Part VI (tablets) with that observed in participants of Part I (capsules) at the same total doses (40 and 160 mg). The PK parameters used for the comparison were Cmax and AUC0-96. The interval of 0 to 96 hours was chosen as it corresponds to the period without activated charcoal administration in Part I and Part VI. Both parameters AUC0-96 and Cmax met the standard bioequivalence criteria with GM ratio for Cmax being 0.985 [90% CI 0.877 - 1.11] and for AUC 0.999 [90% CI 0.901 - 1.11].

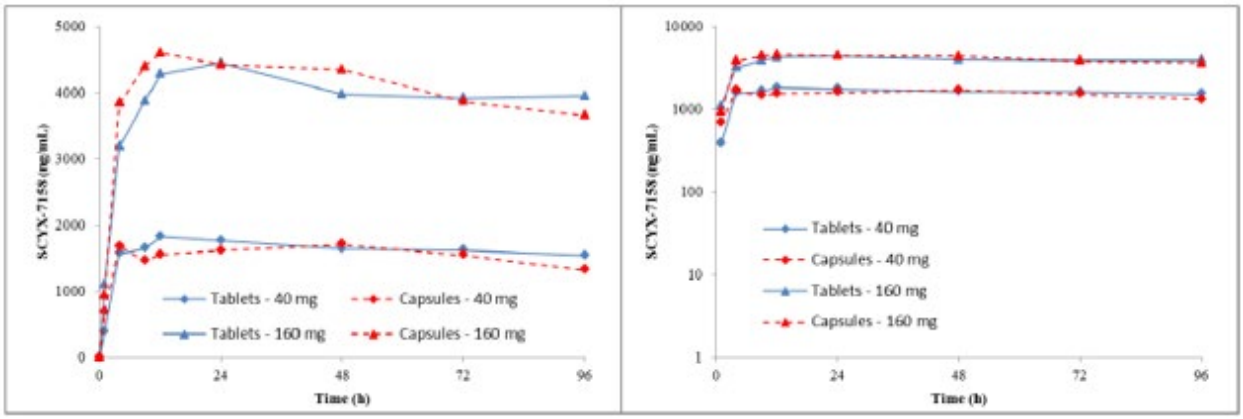


Figure 5. Mean acoziborole plasma concentration versus time profiles after single oral administration of acoziborole doses of 40 or 160 mg as a single tablet (Part VI) or 2 capsules (Part I) over the first 96 hours post-dose.

The different tablet formulations and strengths are homothetic and supportive in vitro dissolution data are assessed in the quality section.

5.2.2.5. Distribution

From the popPk model a moderate apparent central volume of distribution of 109 L (CV=32.1%) was estimated in patients with g-HAT. In the mass balance study the geometric mean Vz/F was 59 L in 6 healthy Caucasian volunteers.

Acoziborole is highly bound to plasma proteins, with a free fraction of around 2% determined by equilibrium dialysis of healthy plasma. Average blood/plasma ratio was estimated to 0.81.

CSF samples from both healthy volunteers and patients with g-HAT show distribution to the CNS with levels corresponding to the free fraction in plasma. This is consistent with animal data.

5.2.2.6. Metabolism

No or slow decline in acoziborole concentrations were observed in all in vitro metabolism systems tested (hepatocytes, S9 fractions, microsomal fractions and recombinant CYPs). In the in vitro CYP phenotyping experiments, some metabolism was observed for CYP1A2, CYP2C8 and CYP3A4. The metabolite SCXY-3109 detected in incubations with human hepatocytes was also formed in incubation without hepatocytes, indicating that oxidative deboronation may also occur non-enzymatically.

From the mass balance study, in plasma the concentration time profile for total radioactivity and acoziborole was very similar. Over 0-336 hours acoziborole was the main component representing 95% of the total radioactivity, only one metabolite was identified in plasma representing 2.3% of the total radioactivity. SCXY-3109 was not detected in the radiochromatograms.

Seven metabolites were detected in urine each representing less than 3% of the dose. In faeces the main metabolite was SCYX-3109 corresponding to 12.3% of the dose. The other identified metabolites represented 2.3% of the dose.

The metabolite profiling was carried out on pooled (0-240 hours) urine and faeces samples representing in total around 58.6% of the dose. The proportions relative to dose were likely underestimated as the excretion of radioactivity was not complete after 10 days (240 hours) (58.6% versus 87.3% on Day 60). The major pathways of acoziborole metabolism identified in humans include: Oxidative deboronation of acoziborole (SCYX-3109) with further glucuronidation or mono-oxidation (15.9% in total). Mono-oxidation of acoziborole (3.5% in total). Considering that only 58.6% of the dose was characterized and assuming the contribution of each pathway is constant over time, each pathway could represent up to 27% and 6% of the dose, respectively, based on a total recovery of the radioactivity of 100%.

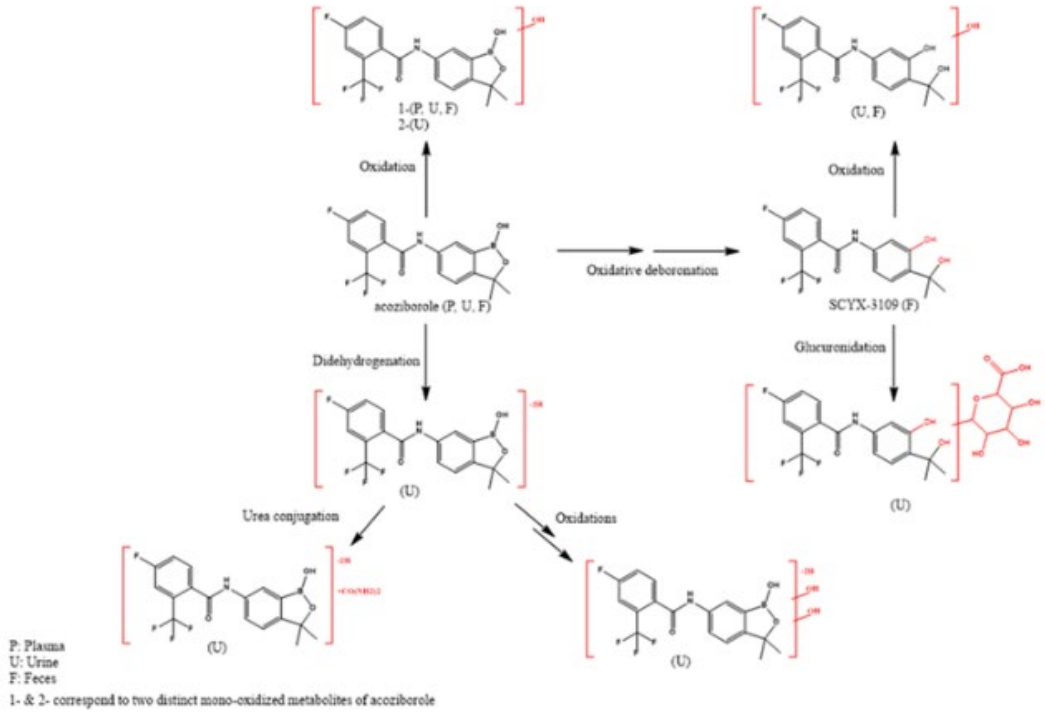


Figure 6. Proposed metabolic pathways for acoziborole

5.2.2.7. Elimination

After the administration of a single oral dose (960 mg) of [14C]-acoziborole to healthy participants, the total recovery was 85 % by day 60 with 74% and 11% of the dose were excreted in faeces and urine, respectively. Mean cumulative excreted dose of total radioactivity was 18.7% and 32.0% in total at 48 and 72 hours post-dose, respectively, the major part being excreted in faeces (17.8% and 30.3% at 48 and 72 hours post-dose, respectively).

Over 0-240 hours 0.6% and 34% of the dose was unchanged parent in urine and faeces respectively. Overall, 34.2% of acoziborole dose was excreted as unchanged acoziborole mainly in faeces (33.6%), whereas about 20.6% of the dose was excreted as identified metabolites and 3.7% as unassigned or unknown).

The t1/2 of plasma radioactivity and acoziborole were 278 and 272 hours, respectively, suggesting that no metabolites had a slower elimination rate limited clearance. This value is consistent with the mean t1/2 estimated in participants with g-HAT (296 h).

The apparent clearance of acoziborole was 0.15 L/h.

5.2.2.8. Dose proportionality and time dependency

Acoziborole geometric mean values for Cmax, AUC0-96, and AUC increased in a less-than-dose-proportional manner. This lack of dose proportionality could be attributed to the low solubility/dissolution of acoziborole. he use of activated charcoal could have contributed to the lack of dose proportionality on AUC.

Acoziborole is given as a single dose. No clinical multiple dose studies have been conducted.

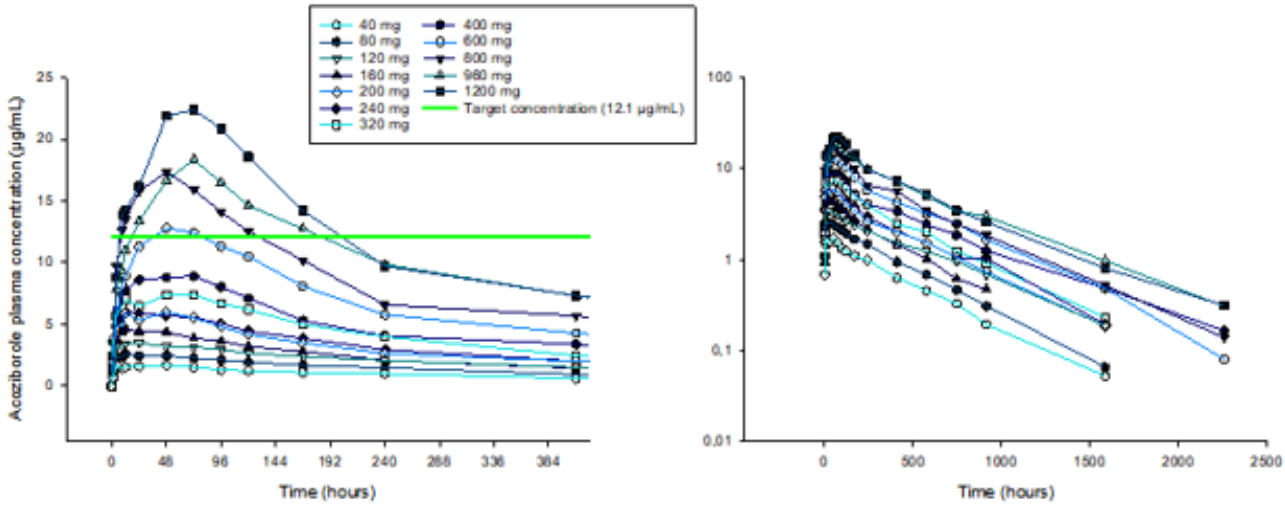


Figure 7. Mean acoziborole plasma concentration versus time profiles after single oral dose administration of 40 to 1200 mg.

5.2.2.9. Pharmacokinetics in the target population

Clinical PK data in the target patient population was collected in the two phase II/III studies. In DNDi-OXA-02-HAT a quite rich sampling schedule was applied whereas sparse data is available from study DNDI-OXA-04-HAT. The observed data indicate similar exposure of acoziborole in the two studies.

Pop-PK modelling, as described in Section 5.2.2.2.1. , was conducted to describe the pharmacokinetics

in study DNDi-OXA-02-HAT. Individual empirical bayes estimates (EBEs) of PK parameters from the final model were used to calculate the AUC0-∞, AUC0-96 , AUC0-240, Cmax and t1/2. A tabulated summary of the obtained PK parameters after single dose of acoziborole (960 mg) in g-HAT patients is presented in the table below.

Table 6: Descriptive statistics of popPK parameters derived from the final model by age group

Parameters	Statistics	Age [15-17 years]	Age > 17 years	All
C_{max} (ng/mL)	N	9	199	208
	Mean (SD)	14069.03 (3758.71)	11458.02 (3291.40)	11570.99 (3345.42)
	GM (CV%)	13571.97 (26.72)	11006.44 (28.73)	11106.68 (28.91)
AUC_{0-96} (h*ng/mL)	N	9	199	208
	Mean (SD)	1176504.44 (313722.84)	961922.51 (275820.94)	971207.31 (280158.14)
	GM (CV%)	1135192.38 (26.67)	924296.44 (28.67)	932552.77 (28.85)
AUC_{0-240} (h*ng/mL)	N	9	199	208
	Mean (SD)	2601444.44 (658930.44)	2165952.11 (614957.22)	2184795.53 (621610.31)
	GM (CV%)	2519841.43 (25.33)	2082798.72 (28.39)	2100036.24 (28.45)
$AUC_{0-\infty}$ (h*ng/mL)	N	9	199	208
	Mean (SD)	5732914.27 (1235021.25)	5193006.04 (1553447.43)	5216367.45 (1542514.41)
	GM (CV%)	5611215.69 (21.54)	4974973.31 (29.91)	5000947.25 (29.57)
$t_{1/2}$ (h)	N	9	199	208
	Mean (SD)	269.36 (38.53)	296.84 (48.68)	295.65 (48.53)
	GM (CV%)	266.84 (14.30)	293.32 (16.40)	292.12 (16.42)

The popPK parameters for acoziborole in g-HAT patients derived from the analysis presented in Section 5.2.2.2.1., were compared to PK-parameters in healthy volunteer's, derived from a different model that were not submitted in the current application.

Table 7. Comparison of popPK parameters (CL/F and V/F) between patients and HV

PK Parameters*	Patients popPK model	HV popPK mode [14]l
CL/F (L/h)	0.240*	0.123
V_2/F (L)	109*	50.4

*Estimated for a typical weight of 70 kg

The geometric mean acoziborole concentrations in CSF measured at Day 11 were 70.3 ng/mL (CV=59.5%) and 83.8 ng/mL (CV=63.4%) for patients with early- or intermediate- and late-stage HAT, respectively. The CSF to DBS ratios were around 1.2% and similar between HAT stages.

5.2.2.10. Special populations

Renal impairment: Acoziborole is given as a single dose only and undergoes very minor renal elimination (<1% of the dose renally eliminated as unchanged drug). No dedicated RI study has been conducted and no restrictions are proposed in the SmPC.

Hepatic impairment: The effect of hepatic impairment on the acoziborole PK profile has not investigated in a dedicated study. Participants with "significant liver disease" were excluded from all Phase II/III studies. In the population PK analysis, liver function variables at baseline were not identified as significant covariates affecting the PK of acoziborole.

Gender: Sex was explored as a covariate during the PopPK analysis and was not a statistically significant covariate for the exposure PK in patients.

Ethnic factors: To evaluate the effect of race/ethnicity on acoziborole PK, the PK parameters observed in participants from multiple studies (DNDiOXA001, DNDi-OXA-02-HAT and DNDi-OXA-03-HAT) were compared, however only 6 subjects of non Sub-Saharan African origin have been treated with acoziborole and though no relevant differences were seen the data set too limited.

Body weight: The mean weigh of the patients included in the study was 53.2 kg (30.0 – 88.0). Data was available for 17 patients weighing 30 – 40 kg. 130 weighing 40 – 60 kg and 54 patients weighing 60- 88 kg. The Observed AUC0-96 and Cmax for the respectively weight span can be seen below.

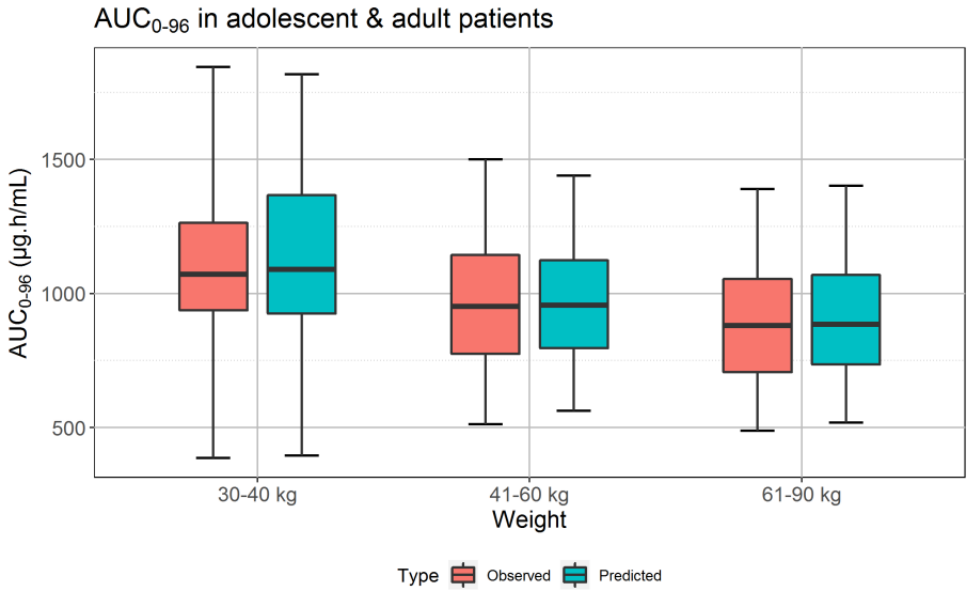


Figure 8. AUC0-96 in adults and adolescent (observed vs predicted) - by bodyweight

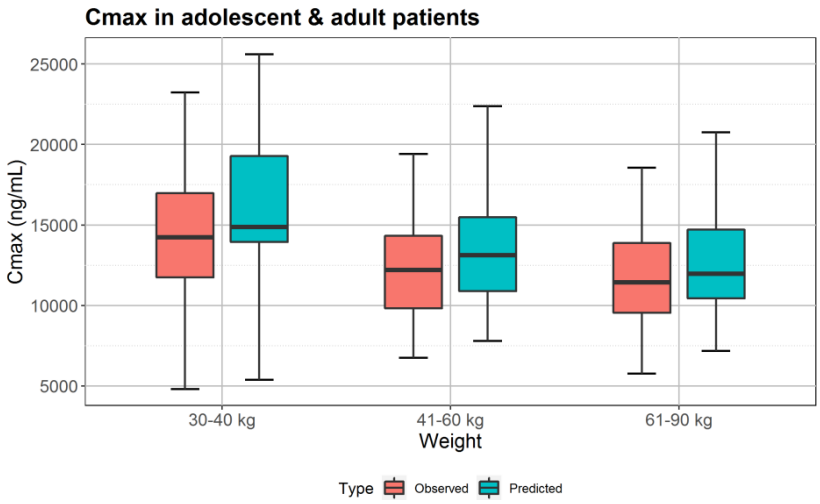


Figure 9. Cmax in adults and adolescent (observed vs predicted) - by bodyweight

Elderly: Age was not found to be a statistically significant covariate during the popPK analysis of (DNDi-OXA-02-HAT). However, only 3 patients ⩾65 years was included in the study.

Paediatric population: The indication for acoziborole is adults and adolescents ⩾12 years. Age was not a significant covariate in the popPK analysis. The observed acoziborole concentration for patients at 15-17 years (n=9) vs adults (n=199) can be seen in Figure 10.

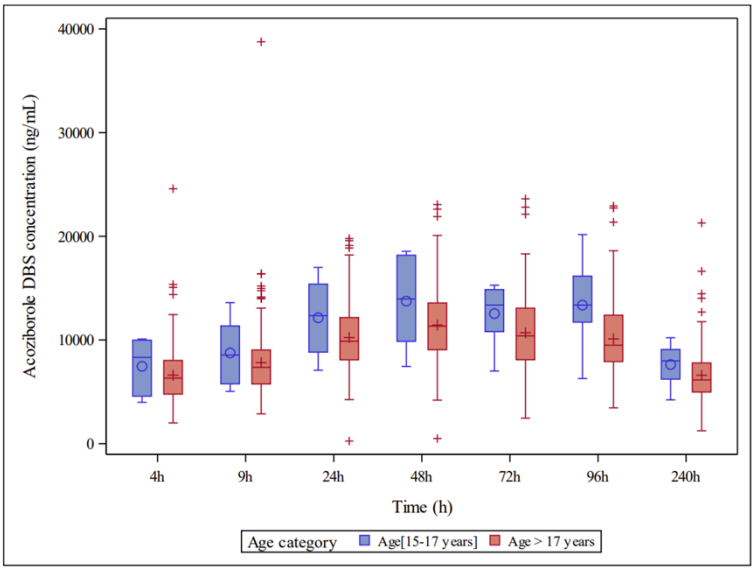


Figure 10. Distribution of Acoziborole (ng/mL) DBS concentration by Age category

5.2.2.11. Pharmacokinetic interaction studies

5.2.2.11.1. Acoziborole as object (victim) of drug-drug interactions

No DDI studies with acoziborole as object has been performed. According to the Applicant acoziborole has a predominant but slow biliary-fecal elimination with limited metabolism. The most significant metabolite identified can be formed by non-enzymatic processes. No single CYP is expected to

contribute to ⩾25% of the total elimination of acoziborole based on the metabolism pathways characterized in vivo. Acoziborole is a substrate of P-gp but given the high intestinal permeability of acoziborole and its high absorption in humans (>70%), the role of P-gp transporters in absoprtion appears to be very limited. Acoziborole is not a substrate of hepatic uptake transporters OATP1B1 and OATP1B3 or of efflux transporter BCRP.

Five patients in study DNDi-OXA-02-HAT received concomitant treatment with strong/moderate CYP inducers rifampicin (n=1) or carbamazepine (n=4), but in all cases the inducer was administered more than 10 days after acoziborole administration when acoziborole levels were approaching LOQ.

5.2.2.11.2. Acoziborole as precipitant (perpetrator) of drug-drug interactions

Table 8. Cut-offs for the evaluation of interaction potential

50×Cmax(u)[a] (µM)	10x Cmax(u)[a] (µM)	10×Inlet Cmax(u)[a, b] (µM)	0.1×dose/250 ml[c] (µM)
43	8.6	137	1046

a Cmax prediction from popPK model of PK in patients with g-HAT after single dose administration of 960 mg is 14.3 ug/ml, fu 0.022 from in vitro data, b ka in vivo 0.289 min-1 from popPK modelling, blood/plasma ratio 0.81 from in vitro data, c dose 960 mg; MW 367 g/mole

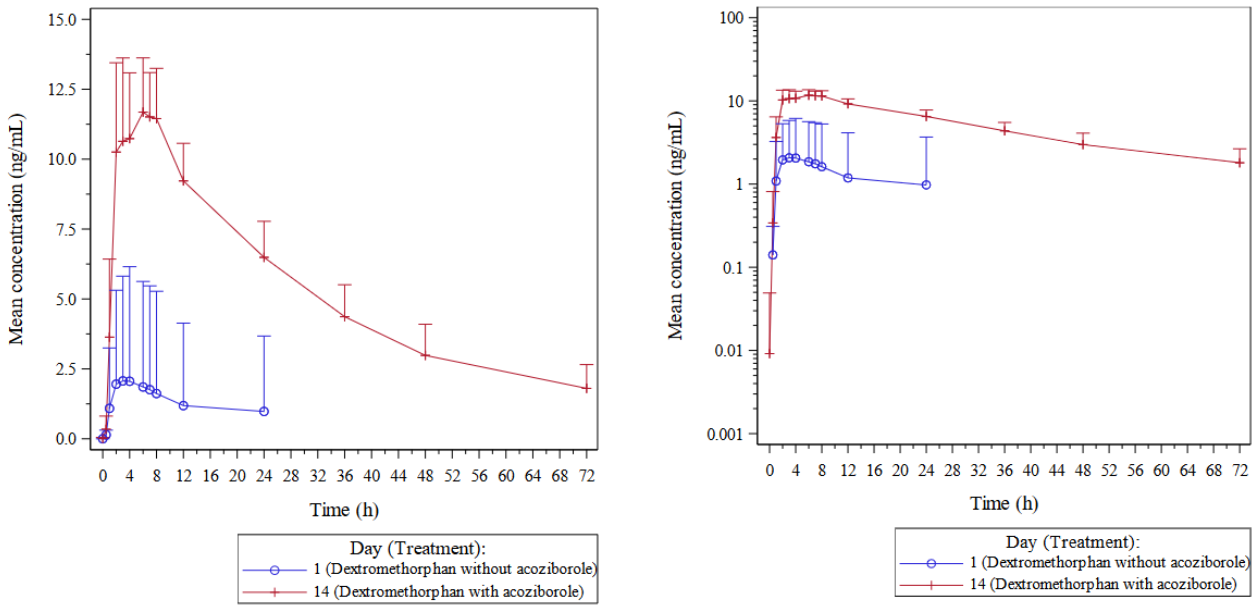
In vitro inhibition of all mandatory CYP enzymes by acoziborole has been investigated. Signals for direct inhibition (IC50/2>50xCmax,u) was seen for CYP2C8 and CYP2D6, and CYP2D6 time dependency was observed. TDI parameters were determined.

Several in vitro induction experiments were performed, and induction (>2 fold increase in mRNA and/or enzyme activity) was observed for all enzymes tested (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9 and CYP2C19 as well as UGT1A1, UGT1A9 and UGT2B7).

In vitro inhibition of all mandatory transporters were also tested. Acoziborole had a signal of in vitro inhibition of BCRP at concentrations relevant for the gastrointestinal tract. In addition, the IC50 for OATP1B1 was below the hepatic inlet cutoff.

One DDI clinical study (**study DNDi-OXA-07-HAT**) was conducted in healthy participants to assess the effects of acoziborole on the PK of sensitive index substrates for CYP2D6 (inhibition) and CYP3A4 (induction). In the first period of the study, a single dose of dextromethorphan and midazolam, respectively, were administered, with one week washout in between. In the second period, a single dose of acoziborole (clinical dose 960 mg) was administered. Two days after, a single dose of dextromorphan was administered, and after 7 additional days (9 days after the acoziborole dose), mioodazolam was given. PK of both acoziborole and the two index drugs (including their metabolites) were measured using validated LC-MS/MS methods.

For dextromethorphan Cmax, AUC0 24, and tAUClast was increased by 13.0-, 20.5- and 35.3-fold, respectively, in the presence of acoziborole. The median tmax for dextromethorphan was delayed (6 hours versus 2 hours) and the geometric mean t1/2 was prolonged (24.3 hours versus 8.4 hours) (Figure 10). For midazolam Cmax, AUC0-24, and AUClast was decreased by 85%, 91%, and 92%, respectively, in the presence of acoziborole. The median tmax for midazolam remained unchanged (0.5 hours), and the geometric mean t1/2 was shorter (3.0 hours versus 6.0 hours). A reduced exposure of midazolam metabolite was also observed, with a geometric mean reduced by 65% for Cmax, 74% for AUC0-24, and 77% for AUClast (Figure 12).



Source: Figure 14.4.3 - 1 and Figure 14.4.3 - 2

Figure 11. Mean (+ SD) dextromethorphan plasma concentrations vs. time profiles following administration of dextromethorphan without and with co-administration of acoziborole (left: linear scale; right: log-linear scale)

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Acoziborole is a 3,3-dimethyloxaborole-6-carboxamide derivative belonging to the benzoxaborole class of compounds, characterized by a boron-heterocyclic scaffold. No specific mechanism of action studies have been performed with acoziborole. The boron atom is essential to the trypanocidal activity of this class of compounds. Acoziborole binds and blocks the active site of CPSF3[4], a metallo-β-lactamase that processes mRNA and facilitates gene expression, resulting in inhibition of the maturation of parasite mRNA. No specific mechanism of action studies have been performed with acoziborole.

5.2.3.2. Primary pharmacology

Primary pharmacodynamics are based on literature references, while secondary pharmacodynamics and safety pharmacology were explored in dedicated studies and are presented and assessed in the Non-clinical AR.

***In vitro* properties**

No metabolite represented more than 10% of the total circulating plasma radioactivity in human. Based on these data, no metabolites were further tested in the CEREP panel or in pharmacology studies.

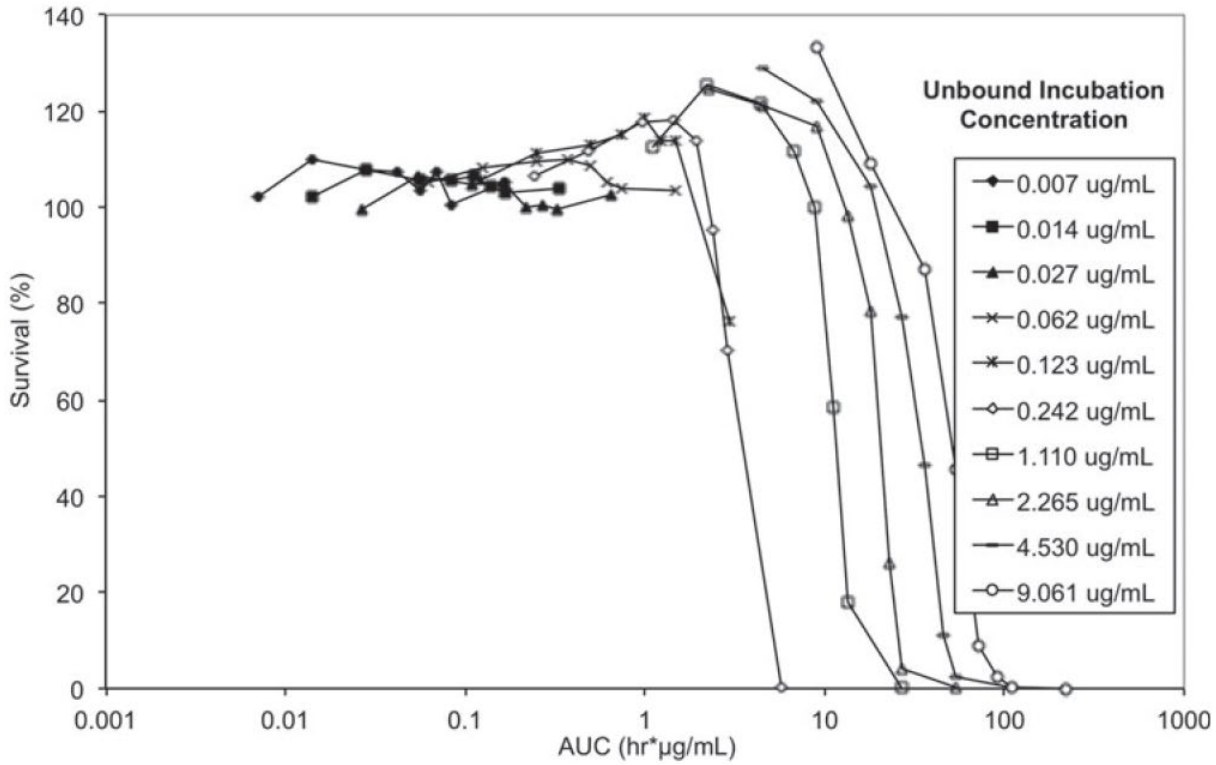
In whole-cell assays[5] where parasitic cell viability was assessed by fluorescence (resazurin), Acoziborole exhibited activity against wild-type *T.b. brucei*, as well as clinical isolates of *T.b. rhodesiense* and *T.b. gambiense* collected in DRC, Tanzania, Uganda and Cote d'Ivoire (dates ranging

[4] Wall RJ, Rico E, Lukac I, Zuccotto F, Elg S, Gilbert IH, et al. Clinical and veterinary trypanocidal benzoxaboroles target CPSF3. Proc Natl Acad Sci. 2018;115(38):9616–21.

from 1960 to 2005), with IC_{50} of 0.065 to 0.363 µg/mL. The MIC for the wild-type *T.b. brucei* S427 strain was approximately two times the measured IC_{50}.

The lowest unbound AUC (5.81 µg×h/mL=0.242 µg/mL x 24 h) associated with a 100% trypanocidal effect (ie, complete and irreversible inhibition) was achieved following incubation with an unbound concentration of 0.242 µg/mL acoziborole for 24 hours[5]. At the next highest concentration (1.11 µg/mL), this target unbound AUC was achieved by 6 hours; however, parasites were able to tolerate the higher concentration for 8 hours without impact on survival, thereby suggesting exposure time rather than absolute concentration maybe the more important factor in determining trypanocidal efficacy.

Figure 12. In vitro irreversibility of trypanocidal effect of acoziborole (survival of T. b. brucei vs cumulative AUC based on unbound concentration)

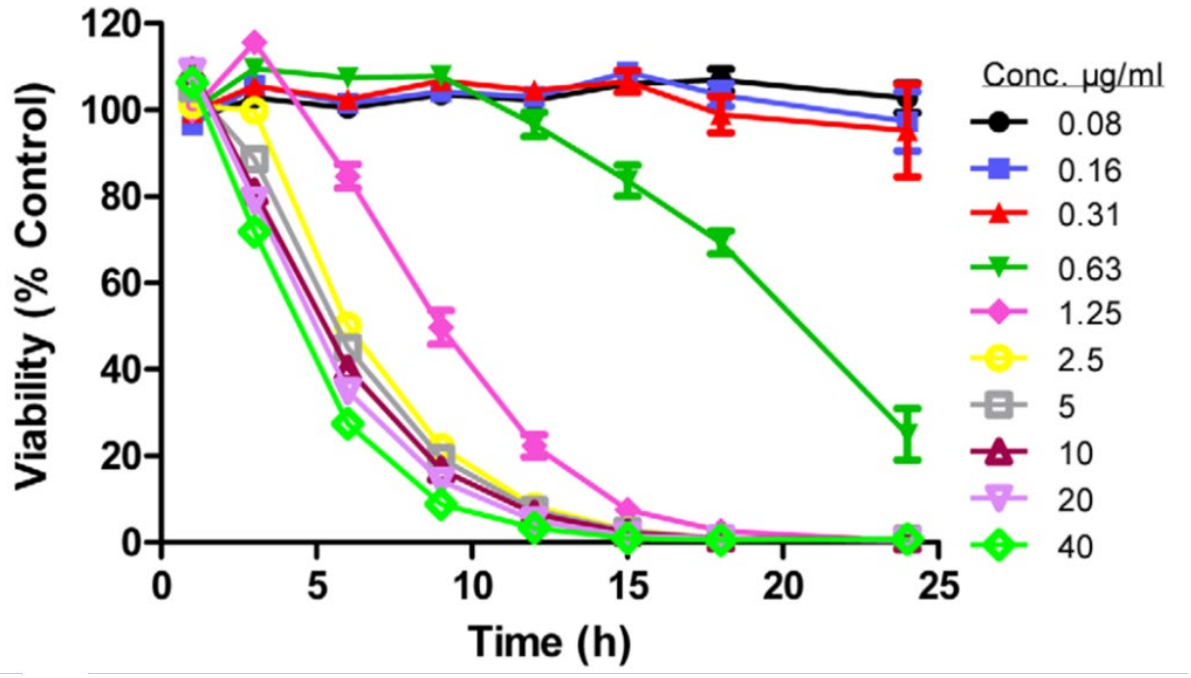


Abbreviations: AUC: area under the concentration-time curve; *T. b.: Trypanosoma brucei*
Source: Wring et al, 2014

In *in vitro* time-kill assays[6] using parasite adenosine triphosphate (ATP) content as an indicator of viability, acoziborole displayed concentration-dependent trypanocidal activity against *T.b. brucei* strain 427, with >50% reduction in viability within 8 hours at concentrations of 1.25 µg/mL (about 2 times the MIC of 0.6 µg/mL) and 99% of parasites killed within 24 hours' exposure.

[5] Wring S, Gaukel E, Nare B, et al. Pharmacokinetics and pharmacodynamics utilizing unbound target tissue exposure as part of a disposition-based rationale for lead optimization of benzoxaboroles in the treatment of Stage 2 Human African Trypanosomiasis. Parasitology. 2014 Jan;141(1):104-18.
[6] Jacobs RT, Nare B, Wring SA, Orr MD, Chen D, Sligar JM, et al. SCYX-7158, an Orally-Active Benzoxaborole for the Treatment of Stage 2 Human African Trypanosomiasis. PLoS Neglected Trop Dis. 2011;5(6):e1151.

Figure 13. In vitro time-kill plot of acoziborole



Abbreviations: Conc.: concentration; h: hour
Source: Jacobs et al, 2011

Shorter exposure (10 to 12 hours) to acoziborole was sufficient to produce irreversible effects on *T.b. brucei* strain 427 survival, with a maximum rate of kill at a concentration requiring about 5 times the IC50. Increasing concentrations above this did not alter the speed of onset.

***In vivo* properties**

In a mouse model of acute trypanosomiasis[5] (intraperitoneal inoculation with 2.5×10^5 parasites of the *T. b. brucei* EATRO 110 strain), mice treated for 4 days with PO doses as low as 5 mg/kg/day starting 24 hours after infection (administered as either 5 mg/kg QD or 2.5 mg/kg BID) exhibited a 100% cure rate at 30 days' follow up. A 100% cure rate (3/3 mice) was also achieved when a single high dose (25 mg/kg) of acoziborole was administered IP.

In a mouse model of chronic trypanosomiasis[5] (CNS, Stage 2) (intraperitoneal inoculation with 1×10^4 parasites of the *T. b. brucei* TREU 667 strain), Berenil (diminazene) was administered as a single 10 mg/kg dose IP on either Day 4 (as positive control) or Day 21 (as negative control). Animals treated with the lowest oral dose (6.25 mg/kg/day) for 7 days were initially cleared of *T.b. brucei* but demonstrated recrudescence of parasitaemia around Day 35 after infection. Meanwhile, an 80% cure rate at 180 days' follow up was observed following ≥ 12.5 mg/kg for 7 days, and a 100% cure rate at 180 days' follow up was observed following ≥ 25 mg/kg for 7 days.

In another mouse Stage 2 HAT model[6], also using the *T. b. brucei* TREU 667 strain, a 100% cure rate was achieved after ≥3 days of dosing at 50 mg/kg, where as no animal was cured after a single dose.

A single PO 50 mg/kg dose achieved an unbound AUC0–24h (18.2 µg×h/mL) in brain tissue that markedly and persistently exceeded the *in vitro* unbound MIC AUC (5.81 µg×h/mL) through 7 days. Animals receiving 25 mg/kg of acoziborole approached the target from *in vitro* studies of unbound AUC0-24h in brain tissue of 5.81 µg×h/mL on Day 1 (4.98 µg×h/mL) and exceeded it on Days 2 to 7 (7.15 µg×h/mL).

Mechanisms of resistance

Point mutation (2) or over-expression (3) (4) of parasite gene *CPSF3* had been shown to yield low-level (around 3 to 6 fold) resistance to the benzoxaboroles in *in vitro* studies. This mechanism should not impact on sensitivity to other available trypanocidal drugs, which act via other pathways.

A reduction in parasite protein sumoylation diminishes the rate at which CPSF3 degradation occurs following binding of acoziborole and this promotes resistance to the drug (5). Furthermore, *in vitro* serial passage for selection of resistance has induced whole-scale shifts in the transcriptional profile rending parasites less sensitive to acoziborole (7). These latter two mechanisms are associated with a significant loss of fitness the precludes them being relevant *in vivo*/ clinically.

There are no *in vivo* study data available. Standardised tests identifying treatment-emergent resistance amongst clinical isolates are not yet available. A Specific High-sensitivity Reporter Enzymatic unLOCKing (SHERLOCK) technology, which enables the distinction between wild-type TbCPSF3 and acoziborole-resistant TbCPSF3 has been developed for epidemiological surveillance.

5.2.3.3. Secondary pharmacology

See section 4. Non-clinical aspects above.

5.2.3.4. Pharmacodynamic interactions with other medicinal products or substances

See 4.4. Pharmacokinetics above.

5.2.3.5. Genetic differences in PD response

No relevant differences in PD between subpopulations are anticipated for this substance with a non-human target.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

5.2.4.1. QTc analyses

Separate QTcF analyses, including concentration-QTc analyses, were performed for studies DNDiOXA001, DNDI-OXA-02-HAT and DNDi-OXA-04-HAT.

Study DNDiOXA001

Study DNDiOXA001 included time-matched PK and ECG measurements on baseline, Days 1 and 4 using replicate ECGs which were used to perform a concentration-QTc analysis. A total of 54 subjects was included in the ECG analysis.

Concentration-response relationship was investigated for SCYX-7158 serum concentrations with ΔΔQTcF using linear mixed models. ΔΔQTcF values were predicted at the observed geometric mean Cmax level for dose levels 160 mg from to 1200 mg. The predicted mean ΔΔQTcF ranged from -5.21 to 0.515 ms and was predicted to be 0.207 for the 960 mg dose.

The study also included digitalized triplicate ECGs for the placebo, 600 mg, 900 mg, 1000 mg and 1200 mg arms at baseline, day 8, day 11 and at multiple follow-up visits. The observed QTc data vs time collected on later time-points are shown in Figure 15.

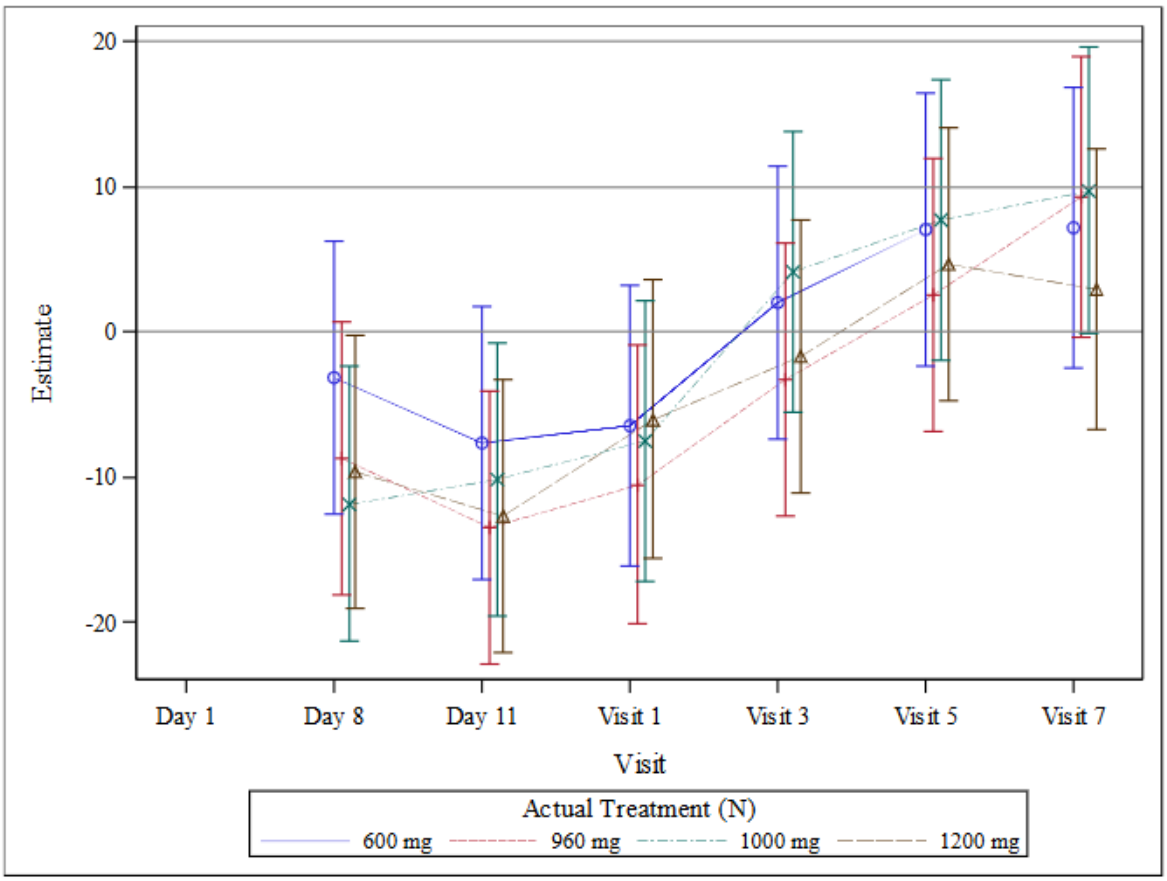


Figure 14. Analysis of Central Tendency of QTcF(ms) - Estimated ΔΔ (Change from Baseline and Placebo) and Two-Sided 90% CI per Dose Level. Visits 1,3,5 and 7 refers to follow up and corresponds to 1 week, 2 weeks, 2 months and 4 months after end of study according to the Study DNDiOXA001 protocol.

Study DNDI-OXA-02-HAT

In study DNDi-OXA-02-HAT, an ECG analysis investigated the effect of acoziborole on ECG parameters in 208 participants with g-HAT. Triplicate ECGs were recorded at baseline and 4, 9, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), and 240 hours (Day 11) after acoziborole administration. DBS samples for acoziborole concentration determination were collected at the same time points as the ones for ECG recordings.

In the central tendency analysis, a decrease in QTcF was observed after a single dose of 960 mg of acoziborole (Figure 15). At 72 hours, mean change from baseline in QTcF was -11.1 ms (SD: 10.2).

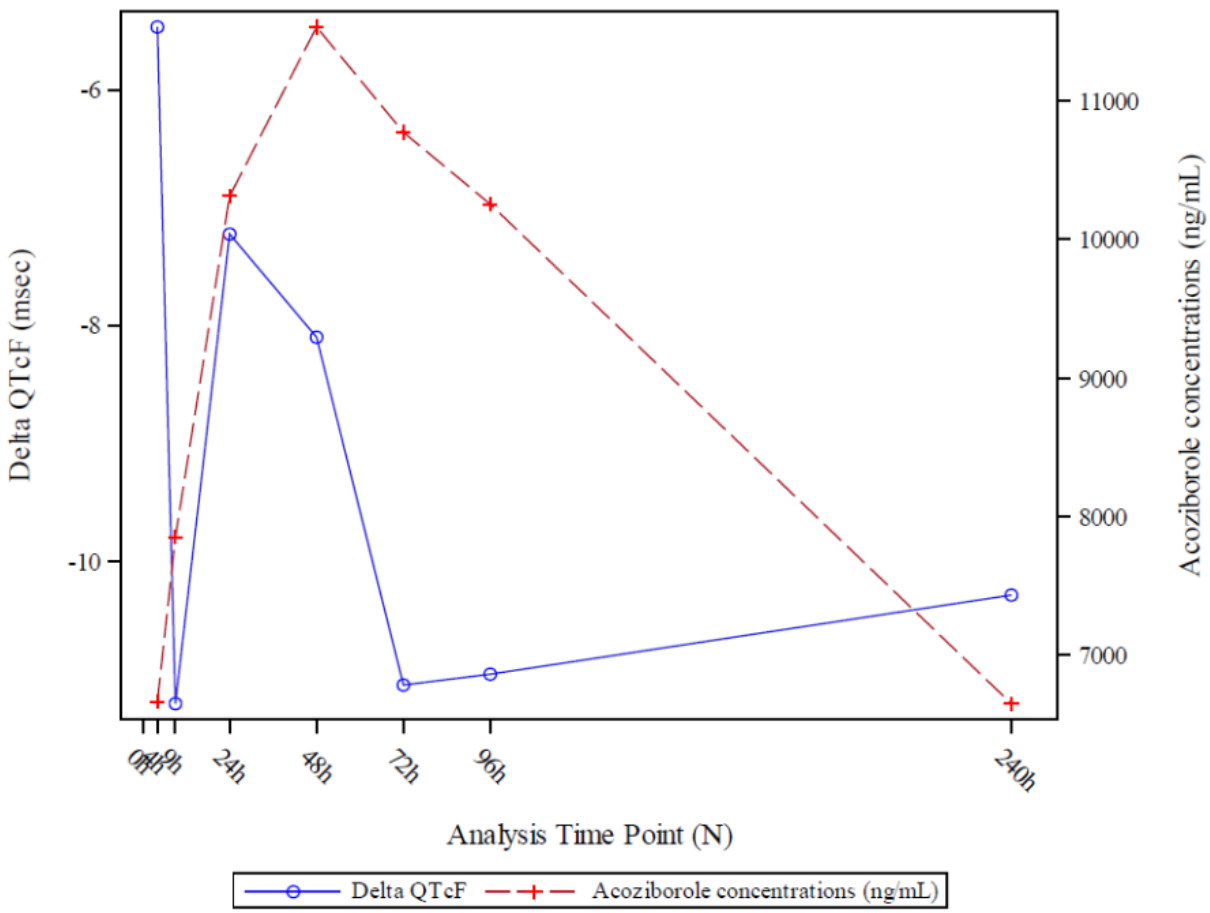


Figure 15. Mean acoziborole concentration versus mean ΔQTcF following 960 mg acoziborole single dose - Study DNDi-OXA-02-HAT

HAT stage was significant on intercept (baseline value), but the number of participants with early- or intermediate-stage g-HAT was unbalanced in comparison with the number of participants with late-stage disease. The slope estimate of the relationship between ΔQTcF and concentration is close to 0 (slope estimate: -0.0001 [95% CI: -0.0003 to 0.0000]). The intercept estimate is -8.12 ms (95% CI: -9.85 to -6.38 ms) (Figure 16).

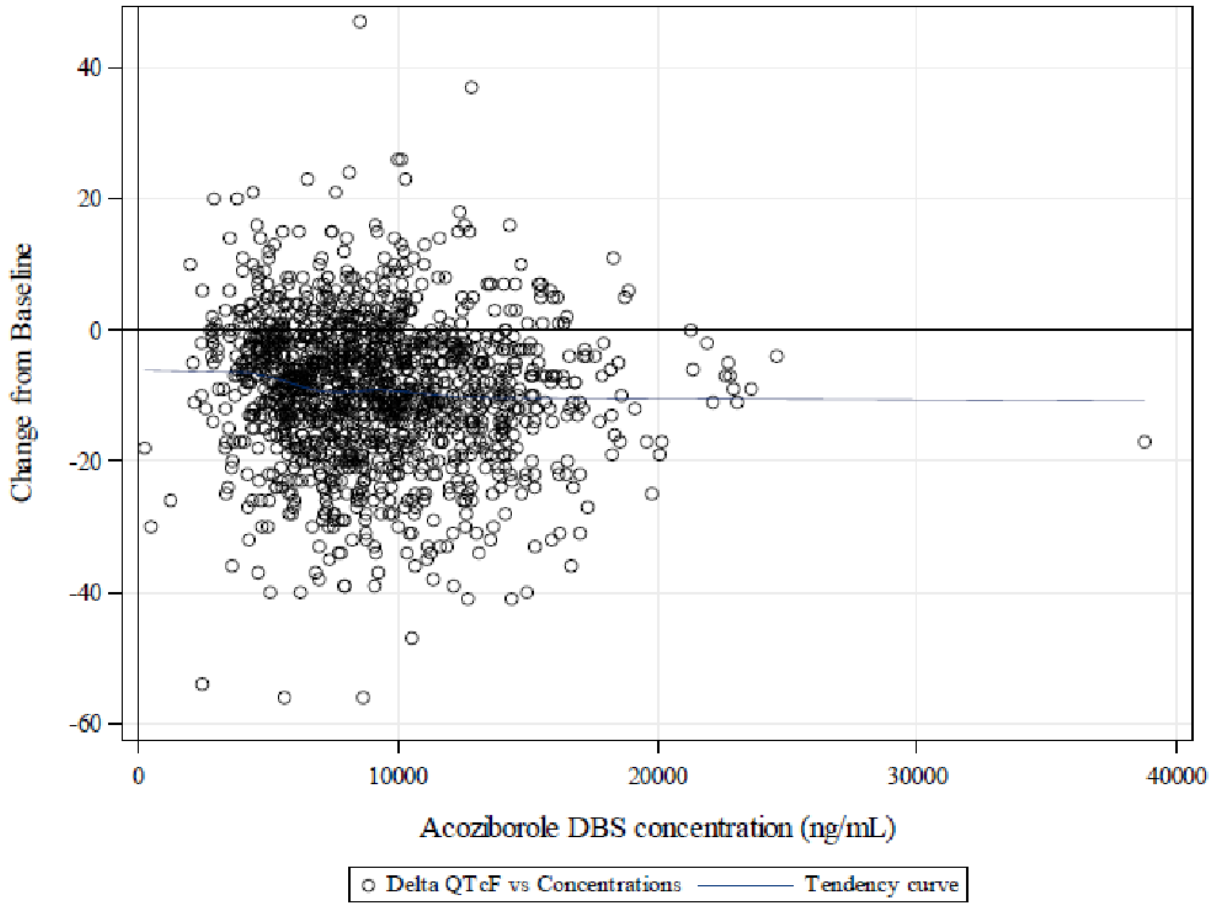


Figure 16. Scatter plots of ΔQTcF versus acoziborole blood concentration following 960 mg acoziborole single dose - Study DNDi-OXA-02-HAT

In line with the central tendency analysis, the model predicted a decrease in QTcF from baseline of -9.28 ms (90% CI: -10.1 to -8.43 ms) at the observed geometric mean blood Cmax (10.5 µg/mL).

Study DNDi-OXA-04-HAT

Study DNDi-OXA-04-HAT investigated effects on the electrocardiogram (ECG) of a single-dose administration of acoziborole compared with placebo to participants seropositive to Human African trypanosomiasis (HAT) caused by Trypanosoma brucei (T.b.) gambiense but non-parasitologically confirmed.

Triplicate ECGs were to be recorded within 1.5 hours of administration of acoziborole or placebo on baseline 96 hours after study drug administration (Day 5). Dry blood spot sampling for acoziborole concentration determination was to be collected at Day 5. Correlation between ΔQTc measurements (ECG assessment) and acoziborole dry blood spot concentrations at Day 5 was estimated.

The ECG analysis set of study DNDi-OXA-04-HAT consisted of 283 treated participants, 215 with acoziborole and 68 with placebo.

The treatment regimen involving a single dose of 960 mg acoziborole in gHAT did not cause an increase in ΔQTcF, but rather decreased it. The analysis of central tendency of QTcF interval, aggregate (ms) – Estimated ΔΔ (change from baseline and placebo) and two-sided 90% CI at Day 5 was -11.5 ms (90%CI: -14.4; -8.7).

Scatter plots of individual acoziborole dry blood spot concentrations versus ΔQTcF are provided in Figure 17.

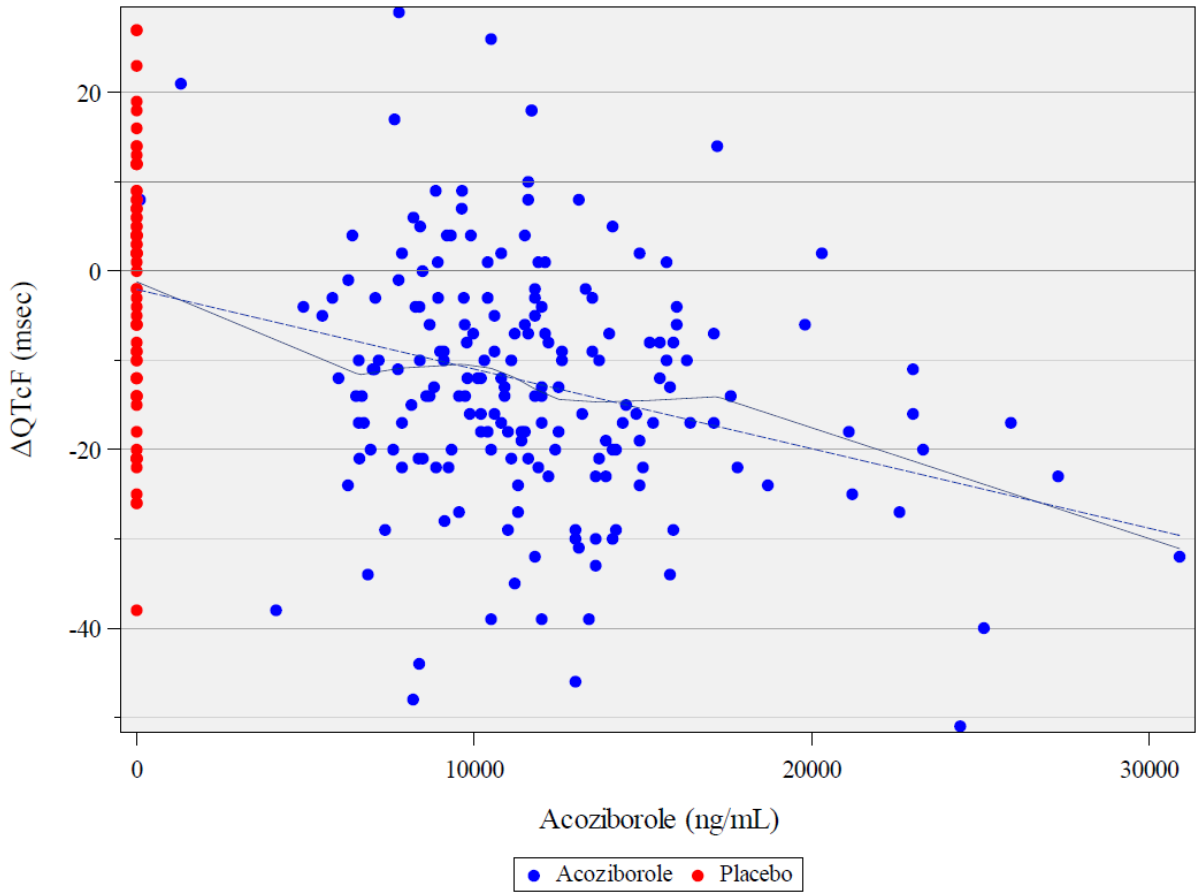


Figure 17. Scatter plot for ΔQTcF interval (top panel) versus acoziborole concentrations. The solid line represents the Loess trend line whereas the dashed line is the result from linear regression.

The concentration-response analysis confirmed the above-noted acoziborole-induced decrease in ΔQTcF. The acoziborole Slope paremter (ms per ng/mL) was estimated to -0.0007 (95%CI: -0.0011; -0.0003). At the observed geometric mean concentration of acoziborole, the estimated decrease in ΔΔQTcF was −10.7 (90% confidence interval (CI): −13.5, −7.85) ms.

5.2.4.2. Exposure-efficacy analyses

The relationship between exposure-efficacy was explored based on data from Study DNDi-OXA-02-HAT. Patients with confirmed treatment failure (HAT relapse) were investigated. Their acoziborole DBS concentrations were superimposed to median, 5th and 95th percentile of concentrations of all other patients, to define if they were underexposed in comparison to the overall population (Figure 17). In the current study, from the 208 patients included there were only 3 of them with a confirmed treatment failure. Overall, no clear common trend could be observed for these 3 subjects although lack of efficacy linked to low exposure could not be totally excluded.

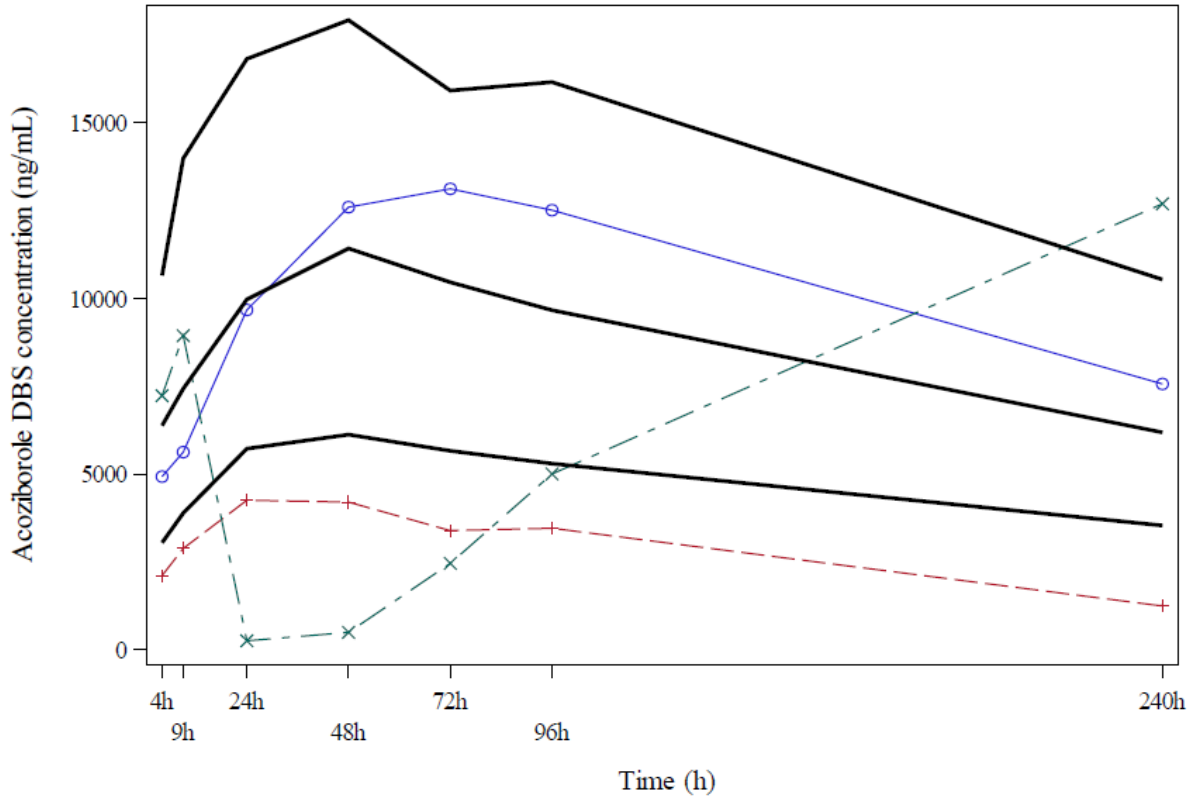


Figure 18. Comparison of Acoziborole (ng/mL) DBS concentration in patients with treatment failure in OXA002 (colored lines) with median, 5th and 95th percentile of other patients (black lines).

5.2.4.3. Exposure-safety

The relationship between exposure-safety was explored based on data from Study DNDi-OXA-02-HAT.

As exploratory purpose, the pharmacokinetic parameters (Cmax, AUC0-96 and AUC0-240) calculated with the parameters obtained from the population pharmacokinetic model were compared with the occurrence of related emergent adverse events (mild, moderate, or severe). Box plots of PK parameters were presented between patients with or without the occurrence of these adverse events (Figure 19).

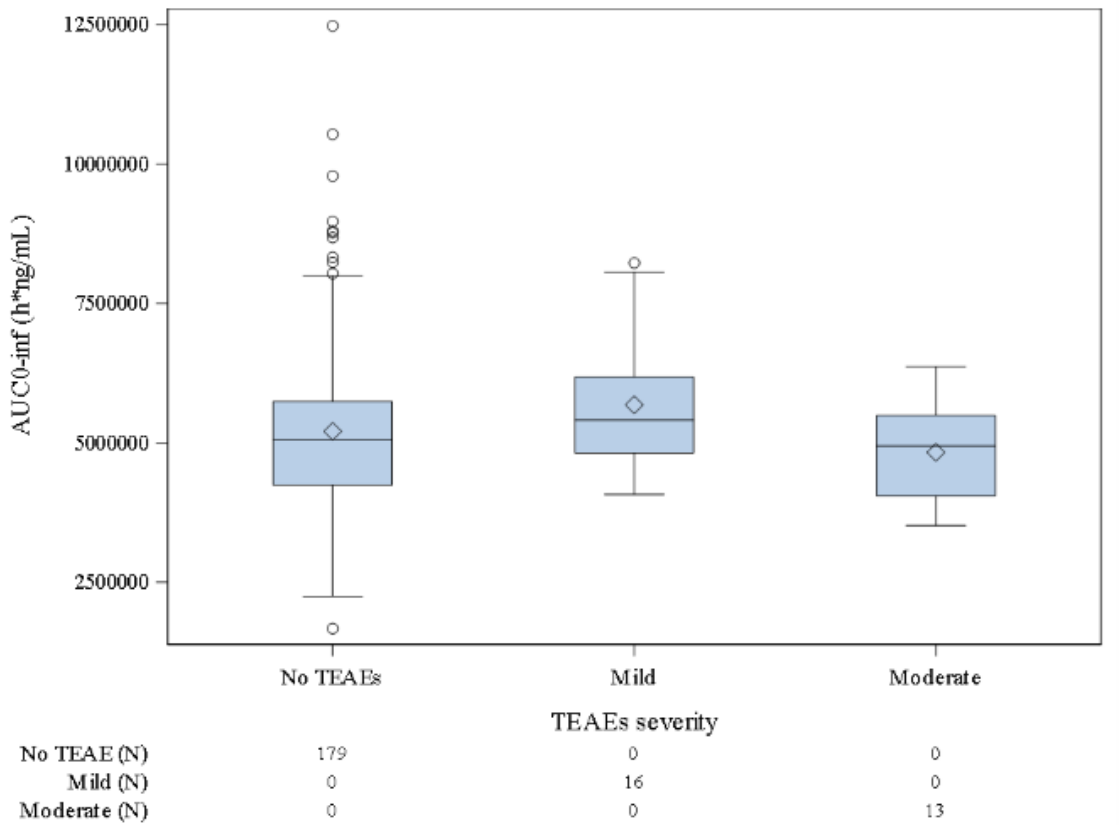


Figure 19. Acoziborole AUC distribution by maximal severity of drug-related TEAE – Study DNDi-OXA-02-HAT

5.2.5. Dose selection and therapeutic window

A single dose of 960 mg is the recommended dose for oral administration which was studied in the pivotal study DNDi-OXA-02-HAT and supportive study DNDi-OXA-04-HAT. This dose regimen was chosen using target acoziborole plasma exposure established based on nonclinical (in vitro and in vivo) data. To better reflect the target site of action, the distribution to CSF were also accounted for.

Safety data was explored in Phase 1 prior to initiating the pivotal study which provided safety data up following administration of 1200 mg.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Pharmacokinetic bioanalytical methods

The bioanalytical methods were validated in line with the ICH M10 guideline. Performance during sample analysis was adequate, samples analysed within established stability and ISR in general acceptable. One exception being ISR for the method using ultrafiltrates (measuring free acoziborole fraction in plasma) however this is considered an exploratory method and issue not further pursued.

Population pharmacokinetic model

The PopPK model is considered to have rather low impact for the overall benefit-risk assessment.

The main role of the PopPK model within this application is for descriptive purposes of acoziborole PK in the target population. The final PopPK model is good enough for describing the PK of acoziborole in patients with HAT from 12 years and above 40 kg.

Of note, the Applicant provided simulations for paediatric patients down to 6 years which is substantially younger than the target population in the current application (adolescents). These results are considered supportive only (data not shown).

The PopPK dataset included a total of 1508 PK observations collected in 208 patients in the target population which is considered acceptable. An overall standard workflow has been used to develop the PopPK model.

A reasonable selection of covariates has been included for the PopPK analysis. The distribution of some of the covariates does not allow for a thorough characterisation. For instance, too few patients were coadministered with rifampicin or carbamazepine to allow a robust characterisation of this as a potential covariate effect. An overall reasonable covariate model development strategy was used where both statistical and clinical significance was assessed by the Applicant. Body weight on clearance and volume using fixed allometric exponents was the only included covariate. Using fixed allometric exponents is considered acceptable given the available data in the current procedure, however, estimated allometric exponents should be explored when more paediatric data becomes available before selecting paediatric in patients <40kg. There was a sign of model misspecification for the body weight-PK relationship according to eta-vs-covariate plots (data not shown). Dosing in patients <40kg is out of scope for the current procedure and thus, this concern related to allometric scaling is not pursued further in the current application (see additional discussion under Special Populations).

Physiology based pharmacokinetic models (PBPK)

A PBPK model was developed to evaluate the acoziborole DDI potential. As no clinical DDI data were available to verify the model prediction for the majority of the enzymes involved, the model is not considered qualified for its purpose. In addition, the uncertainty for the model to be able to predict complex interactions involving both inhibition and induction, as well as transporters, is judged to be too high. As data on the interaction with sensitive CYP3A4 and CYP2D6 probe substrates are available, the model is not considered to be needed in order to guide labelling for interactions involving solely these enzymes. The PBPK model is consequentially not presented in detail here.

The Applicant also submitted a PBPK/PBBM model to support the administration of acoziborole with or without food (data not shown). Several limitations were identified in the model that questions its ability to accurate describe and predict the absorption of acoziborole. Critically, the model could not be qualified with clinical data with food. As a food effect on the absorption cannot be excluded based on the available information, acoziborole should be taken without food as stated in the SmPC section 4.2.

ADME

Acoziborole is an antiprotozoal drug for which exposure in the CNS is of importance. Based on non-clinical data a free CSF AUC0-24 of 5.81 µg/mL*h is required for at least 3 consecutive days for in vivo cure. In human studies measuring CSF concentration the unbound plasma concentration of acoziborole correlates with the CSF concentrations, indicating diffusion over the BBB and that transporter proteins do not play a major role in the distribution to the CNS. The proposed clinical dose of 960 mg will provide a plasma exposure 1.5-fold over the targeted exposure for at least 3 days.

Acoziborole drug substance is practically insoluble in aqueous media at pH 1.2, 4.5 and 6.8. In medium simulating fed conditions the solubility is approximately twice that in medium simulating fasted conditions. In vitro permeability is relatively high and likely all substance in solution is relatively quickly absorbed and the absorption limited by solubility. In the SAD-study acoziborole appeared rapidly in plasma (1 hour post-dose). Its absorption was slow and prolonged, with a tmax reached around 72 hours (range from 48 to 96 hours) for the 960 mg dose, however the sampling was sparce and the tmax thus not precisely determined. At lower doses tmax was in general shorter, for 20 mg ranging between 3-24 hours.

The effect of food on the bioavailability of acoziborole has not been investigated in a clinical study. In all conducted clinical studies acoziborole has been administrated in fasted state. As solubility is twice as high in simulated fed state and absorption likely limited by solubility, a more rapid absorption and faster and higher Cmax could be the result. The opposite scenario with lower exposure could be the result if acoziborole would bind to constituents of the food hindering absorption. Several limitations were identified in the PBPK model used to support administration with food. Its ability to accurately describe and predict the absorption of acoziborole is questioned. Critically, the model could not be qualified with clinical data with food. Overall, the effect of food on the PK of acoziborole is unknown and there are uncertainties if certain types of food could lead to relevant changes in absorption and exposure. In the SmPC the recommendation regarding food is based on the restrictions used in the pivotal phase-3 trial, i.e. not consuming food at least 2 hour before and 2 hours after administration of acoziborole. This is acceptable.

The elimination of acoziborole is slow with a half-life ranging between 267-409 hours for all doses. There are indications of enterohepatic recycling, at least for lower doses, however co-administration of activated charcoal during the elimination phase had a limited effect. Also in the studies in dogs charcoal could reduce half-life by 50% at low acoziborole doses but was ineffective at higher doses. Enterohepatic recycling does not seem to be of great importance at the clinical dose.

The mass balance study was affected by covid restrictions limiting planned sampling. Still the total recovery over 60 days were acceptable being 85% with 74% of the dose excreted in faeces and 11% in urine. Metabolite profiling has only been conducted at early time points less than one half-life of acoziborole, rendering the quantification of these pathways uncertain (see discussion below). The mean total radioactivity in plasma exhibited a qualitatively similar concentration-time profile to that of acoziborole in plasma indicating that no significant metabolites were present in the systemic circulation. Over 0-336 hours acoziborole was 95% of the total radioactivity. Only one metabolite was identified in plasma representing 2.3% of the total radioactivity. SCXY-3109 was not detected in the radiochromatograms. It is agreed that there are no major plasma metabolites formed by acoziborole.

Metabolite profiling in excreta was only performed using a pool from samples between 0-240 hours. At this time total recovery was 58.6 % of the dose and parent represented almost 34% of the dose in faeces. The Applicant provides a calculation for the metabolic pathways, assuming the contribution of each pathway is constant over time and 100% recovery, concluding that the oxidative deboronation pathways could amount to 27% of the dose. Applying this method also for parent, 57% of the dose is estimated to be excreted unchanged in faeces. Biliary excretion appears to be an important elimination pathway of acoziborole.

Target population

The Applicant used PopPK modelling to describe PK in the target population which is considered reasonable. The results from the phase II/III study (DNDi-OXA-02-HAT) indicates that the exposure of acoziborole is slightly lower in patients than in healthy participants. After correction by the blood/plasma ratio (0.81), no relevant difference was observed between acoziborole exposures observed in participants with g-HAT and those observed in healthy participants. No IV data were

available to provide information about the bioavailability and fraction absorbed in the respective population this is acceptable.

The Applicant has included information on PK in the target population based on the PopPK model. This includes AUC and Cmax mean estimates and %CV.

Mean CSF to DBS ratios were 1.3% in participants with early- or intermediate-stage g-HAT and 1.5% in participants with late-stage g-HAT. The CSF to DBS ratios were consistent between HAT stages, suggesting that an advanced g-HAT stage does not alter BBB permeability for acoziborole.

Special populations

Considering the single dose posology, the low renal and metabolic elimination of acoziborole the absence of a RI study is acceptable.

The main elimination pathway for acoziborole is hepatobiliary, including slow metabolism and biliary excretion. A dedicated hepatic impairment study has not been conducted and no patients with significant liver disease were included in the clinical studies, overall the prevalence of hepatic impairment among screened participants was low according to the Applicant. The proposed SmPC states that acoziborole is not recommended in patients with severe hepatic impairment and/or with clinical signs of jaundice or ascites. The clinical signs may also include certain patients with child pugh B (moderate HI) which is considered acceptable.

A popPK approach is acceptable for exploring sex as a covariate on acoziborole PK.

The target population is mainly people living in areas affected by the disease, ie sub-Saharan Africans. The limited PK-data available in other ethnicities are acceptable. Though hampered by the limited data no differences in PK based on ethnicity are obvious.

Body weight was explored as a covariate during the PopPK analysis. Body weight was included on PK parameters clearance and volume of distribution using fixed allometric exponents.

The target population includes paediatric patients (adolescents). The main difference between adults and adolescents that could lead to a difference in acoziborole PK is the expected lower body weight in adolescents than adults. Since acoziborole PK parameters clearance and volume of distribution increase by body weight, adolescents with low body weight may get higher exposure than what has been observed in Study DNDi-OXA-02-HAT when treated with the proposed dose of 960 mg which could lead to safety concerns.

The indication includes adolescents with a body weight ≥ 40 kg. The B/R of the proposed dose (960 mg) is too uncertain in paediatric patients <40 kg based on the totality of evidence. The key concern is that paediatric patients <40 kg would be over-exposed at the proposed dose which could result in a potential safety concern in this subpopulation.

Adolescents below 40 kg have numerically higher exposure (AUC and Cmax) compared to patients >40 kg which could translate to increased safety concerns which could affect the B/R in this subpopulation. There are too few patients <40 kg in the clinical database (n=17) to support that 960 mg has positive B/R in paediatric patients <40 kg. In addition, there was a trend in the PopPK goodness-of-fit-plots (eta-vs-covariate plots for body weight-CL and body weight-V) which suggested a model misspecification for the body weight-PK relationship.

Furthermore, the Applicant has provided paediatric PK simulations as supportive evidence. The simulations explored different paediatric posologies depending on body weight. The simulations indicated that a lower dose than 960 mg would be more appropriate in paediatric patients weighing <40 kg. This further reinforces the concern that 960 mg may be inappropriate in paediatric patients <40kg. It is not possible to recommend a lower dose than 960 mg in paediatric patients <40 kg

based on the data included in the current procedure; to support a lower dose than 960 mg in patients <40 kg would require observed paediatric PK data where lower doses have been studied. According to the dossier, a clinical study (DNDi-OXA-05-HAT) studying acoziborole in children weighing 10 – 40 kg is ongoing. The Applicant is expected to submit a variation with an updated dosing regimen for this lower weight range after the completion of this study (estimated to 2026).

Of note, the current PopPK model is not considered sufficiently robust to be used as pivotal evidence to support a lower-than-studied paediatric posology. Thus, no updated PopPK model is requested.

Adolescents from 12 years are included in the indication (SmPC section 4.1), with the posology of 960 mg. No clinical data from adolescents <15 years were submitted. However, it can be assumed that there are no clinically relevant differences in the acoziborole PK and PKPD behavior between a 12 year-old and a 15 year-old patient. Given the importance of body weight rather than age for adolescents, and that a body weight 40 kg cut-off is restricting the posology, an age cut-off of 12 years in SmPC section 4.1 is supported and could result in even more patients benefitting from acoziborole.

Limited PK-data is available in subjects >65 years of age. Only 3 subjects were included in the popPK-analysis from the patient study. No subjects were elderly in the studies in healthy volunteers.

Intra- and inter- individual variability

The total variability (CV%) of the derived population PK parameters in participants with g-HAT ranged between 16.4% and 29.6%. The PK variabilities (CV%) observed on Cmax and AUC parameters in the target population were around 29% to 30%.

Drug-drug interactions

Victim aspects

No DDI studies were performed with acoziborole as a victim. Metabolism appears to be of limited importance for the elimination of acoziborole, and thus the risk for interactions with enzyme inhibitors is considered limited. The role of different transporters in the biliary excretion of acoziborole is however not clear, and a discussion regarding the risk for interactions with transporter inhibitors is anticipated (see elimination section 5.2.2.7.). There is no conclusive data on the potential effect of inducers on acoziborole exposure, but given that acoziborole itself is a strong inducer it appears unlikely that additional induction would significantly alter the exposure of acoziborole.

Perpetrator aspects

Acoziborole has a strong potential to interact with many concomitantly used drugs. It is a strong inducer and also a strong inhibitor of CYP2D6, and given the long half life of acoziborole the interaction risk may last for several months despite the single dose administration.

Giving proper and actionable information about this in the SmPC is a challenge. A general description of the interaction mechanisms and time course, together with recommendations for substrates of each enzyme/transporter are now given in the SmPC, and it is emphasised that the SmPC for concomitantly used drugs need to be consulted regarding co-administration with enzyme inducers and CYP2D6 inhibitors. To ensure that the personnel distributing acoziborole takes the interaction risks into account, the SmPC advices that patients treated with chronic concomitant medications should be evaluated by a health-care provider for drug-drug interactions prior to prescription. The interaction risk is also considered as an important identified risk in the RMP safety specifications.

The Applicant has performed an adequate set of in vitro inhibition and induction experiments for

acoziborole. In vitro ***enzyme inhibition*** was observed for CYP2C8 and CYP2D6. A strong inhibitor effect on CYP2D6 was confirmed in a DDI study with dexamethasone (DNDi-OXA-07-HAT). In the clinical DDI study 1 participant was ultrarapid metabolizer (UM), 15 participants were extensive metabolizers (EM), and 4 were intermediate metabolizers (IM). Although CYP2D6 poor metabolizers were excluded, the high variability in dextromethorphan plasma exposure (with CV% of 184.0, 230.4 and 286.8, for Cmax, AUC0-24 and AUC0-t, respectively) that was observed could be explained by the heterogenous participant population, from CYP2D6 ultra-rapid to intermediate metabolizers. Given that the in vitro Ki observed for CYP2C8 (32 uM) was close to the regulatory cutoff 50xCmaxu (43 uM), and that the CYP2C induction is expected to be large for a strong CYP3A4 inducer, it is considered unlikely that CYP2C8 inhibition would be clinically relevant. Based on this, it is also considered unnecessary to mention the in vitro inhibitory signal in the SmPC section 5.2. The ***in vitro induction*** experiments revealed signals of in vitro induction at relevant concentrations of all CYP isoforms tested (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9 and CYP2C19), and the clinical study with midazolam (DNDi-OXA-07-HAT), revealed strong CYP3A4 induction. The study was design to maximise the induction effect, where PBPK simulations predicted the interaction between acoziborole and midazolam to be maximal around Day 8 (due to the activity CYP3A4) following acoziborole administration and sustained for several weeks after. Thus, midazolam was given on Day 8 in Period 1 (without acoziborole) and on Day 21 in Period 2, *i.e*. 9 days following oral single administration of acoziborole. This was considered reasonable.

There are no clinical DDI data on the induction effect on substrates of other enzymes than CYP3A4, or transporters.(for example 2C-enzyme(s), Pgp and potentially CYP1A2, CYP2B6 and UGT1A1), and there is no clinical data on the duration and time course of induction. Additional clinical data would potentially allow more specific recommendations in the SmPC, but at present it is agreed that broad warnings regarding the induction risk need to be given in the SmPC. The SmPC for the concomitant drug needs to be consulted for the recommendations together with strong inducers.

The in vitro ***transporter inhibition*** experiments revealed a limited in vitro inhibition potential, with inhibition signals of BCRP (gastrointestinal tract) andOATP1B1 (hepatic inlet). A warning for BCRP inhibition is included in the SmPC which is supported Given that a risk for OATP1B1 inhibition was evident only using the hepatic inlet concentration cutoff, the risk for a clinically relevant interaction during absorption is considered low as acoziborole is only administered as a single dose.

The Applicant proposes that the interaction effect on enzymes (induction) and CYP2D6 (TDI) may persist for up to 3 months, based on acoziborole half-life and enzyme turnover rate. This is considered a relevant and fairly conservative estimation of the duration of DDI risk.

Drugs whose plasma levels are expected to decrease together with acoziborole, and where the therapeutic effect is very important for the patient and compensatory dose adjustments to maintain efficacy cannot be performed, need to be contraindicated together with acoziborole given the strong induction effect. In general, medicinal products contraindicated with rifampicin also need to be contraindicated with acoziborole, which has shown a similar degree of inducing capacity. The Applicant has adjusted the list of contraindicated drugs to focus on drugs that are used in the intended patient population, which is supported. The antimalarial agents artemether and lumefantrine are contraindicated with rifampicin. Given that the induction effect is expected to gradually decrease with time, and artemether-lumefantrine can be used with moderate inducers with appropriate monitoring, and the clinical need for immendiate antimalaria treatment can be large in endemic countries, it is however considered reasonable to restrict the contraindication to the first month after acoziborole administration. To make the prescriber aware of the remaining (weaker) induction effect on the metabolism of artemether and lufantrine 1-3 months after acoziborole administration, a text of the SmPC in section 4.5 has been added.

Primary pharmacodynamics

Primary pharmacodynamics are based on literature references. The available nonclinical primary pharmacology data show that acoziborole has time- and AUC/MIC-dependent trypanocidal activity against the protozoan parasites *T.b. gambiense* and *T.b. rhodesiense* in whole-cell *in vitro* assays, with complete elimination of parasites from the culture within 24 hours' exposure at a MIC of 0.6 µg/mL and 100% *in vivo* efficacy in a mouse model of chronic Stage 2 disease with a sustained brain tissue AUC0-24h above the target AUC of 5.81 µgxh/mL.

There are no *in vivo* data on mechanisms of treatment emergent resistance. *In vitro* data suggest one potentially credible mechanism of resistance via point mutation or over-expression of acoziborole's target, TbCPSF3. These mechanisms result in modest reductions in drug sensitivity *in vitro*, typically on the order of ~3-fold. This mechanism should not impact on sensitivity to other available trypanocidal drugs, which act via other pathways. Standardised tests identifying treatment-emergent resistance amongst clinical isolates are not yet available. Resistance surveillance and the duty to report new emerging patterns that might impact the product's benefit-risk balance remain, as always, the responsibility of the MAH in the post-marketing setting.

QTcF analyses

The characterisation of the pro-arrhythmic potential of acoziborole currently lies upon non-clinical investigations (hERG activity and in vivo cardiovascular effects on beagle dogs) and clinical data generated during the Phase I and II/III program of the drug development.

The Applicant reports an inhibitory effect on hERG activity at dose >100 mM (i.e. 36.7 µg/ml). No in vivo effects on cardiovascular parameters were observed in the studied animal models. However, in humans, the drug displayed a shortening effect on the QT interval.

Separate QTcF analyses, including concentration-QTc analyses, were performed for studies DNDiOXA001, DNDI-OXA-02-HAT and DNDi-OXA-04-HAT.

The QTcF analyses suggests that acoziborole shortens the QTc interval with a mean shortening of up to ~10-12 ms. However, no clear exposure-response trend between acoziborole concentration and QTc shortening were evident.

The by time-point analysis for central tendency in Study DNDiOXA001 indicated a mean shortening of the QTc interval of up to ~12-14 ms on Day 11 for the proposed dose of 960 mg. The data also indicated that the decrease in QTcF is transient, with a gradual return to baseline following ~1-2 months after dose administration. However, the sample size per dose group were limited and the confidence intervals were wide and overlapped between the dose groups. Furthermore, the data later than Day 4 is further hampered by the different use of no activated charcoal across doses leading to different elimination rates. The by time-point analysis for central tendency in Study DNDI-OXA-02-HAT suggested a mean shortening of the QTcF interval of -11.1 ms (SD: 10.8) at 72h. The central tendency analysis of Study DNDI-OXA-04-HAT suggested a mean shortening of the QTcF interval of -11.5 ms (90%CI: -14.4 to -8.7) on Day 5 (placebo- and baseline-corrected), however the corresponding standard deviation (SD) was not reported. The corresponding mean (SD) change from baseline value without placebo-correction were -12.8 ms (SD: 13.3).

Time-matched QTcF baseline correction was only applied for the Days 1 and 4 data in study DNDiOXA001. For the other time-points and studies, it's unclear whether standardization of the clock time of the ECG sampling (such as in the morning) was applied which adds further uncertainty to the QTcF estimates, since QTcF may be subject to diurnal variation. Of note, in Study DNDI-OXA-02-HAT, there is a distinct decrease in the QTcF of ~11 ms at 9 hours following dose administration, but this should be interpreted with caution due to the potential influence of diurnal variation. Placebo-

correction was applied in Study DNDi-OXA-04-HAT and Study DNDiOXA001 but not for Study DNDI-OXA-02-HAT which adds further uncertainty.

Concentration-QTc analyses were performed for Studies DNDiOXA001, DNDI-OXA-02-HAT and DNDi-OXA-04-HAT. Although the concentration-QTc analyses indicated a rather weak tendency of shortened QTc interval with increasing acoziborole concentration, the results should be interpreted with great caution since several considerable limitations have been identified; There appear to be an effect delay in the QTcF shortening which has not been accounted for. Only a single dose level was studied in the patient studies which is insufficient to robustly conclude that there is an exposure-response trend. Different doses were studied in healthy volunteers where the sample size was very limited and the highest dose studied was 1200 mg which is not considered supratherapeutic exposure in the context of a concentration-QTc analysis.

From a regulatory perspective, no specific guidance is available in support of the definition of clinically relevant thresholds of concern for a QT-shortening effect. In principle, the same strategy adopted in the evaluation of medicinal products with a QT-prolongation risk can be applied to acoziborole, encompassing a totality of evidence approach based on non-clinical and clinical evidence.

Exposure-response analyses of efficacy and safety

The exposure-response analyses are supportive only with very limited impact on the benefit-risk assessment. The exposure-response analyses were not indicative of any relevant exposure-response relationships. The exposure-response analyses have the major limitation that only a single dose level was studied for each regimen (i.e. lack of dose ranging data). This implies that the observed exposure range is too narrow to allow a robust characterisation of the underlying exposure-response relationships. Given that the efficacy and safety data are pivotal for the benefit-risk assessment, any noted limitations with the exposure-response analyses will not be pursued further.

Dose selection

The proposed dose of 960 mg has been studied in the pivotal study and is considered overall reasonable. The dose was initially selected to achieve exposure targets based on efficacy from in vitro and animal studies whilst also accounting for safety aspects from early studies in healthy volunteers. For further discussion, see also Overall discussion and conclusions on clinical efficacy.

5.2.6.2. Conclusions

Acoziborole has quite unusual PK-properties with slow absorption (tmax of 48-96 hours) and a long elimination half-life of 12 days. Acoziborole has a strong potential to interact with many concomitantly used drugs and given the long half life of acoziborole, the interaction risk may last for several months despite the single dose administration.

Based on the current state of knowledge, the uncertainties regarding resistance development are outweighed by the clinical benefit demonstrated.

The dose justification is considered acceptable.

5.3. Clinical efficacy

5.3.1. Dose response studies

No formal dose-finding study in patients was conducted.

The Applicant describes selection of a therapeutic dose of 960 mg (3 x 320 mg) to be tested in pivotal clinical studies using target plasma acoziborole exposure derived from non-clinical primary pharmacology studies, PK and safety/tolerability data obtained from healthy participants administered single doses up to 1200 mg, and the observed blood brain barrier penetration of acoziborole in non-human primates and healthy volunteers.

See detailed discussion in 5.2.5. Dose selection and therapeutic window, above.

5.3.2. Main study

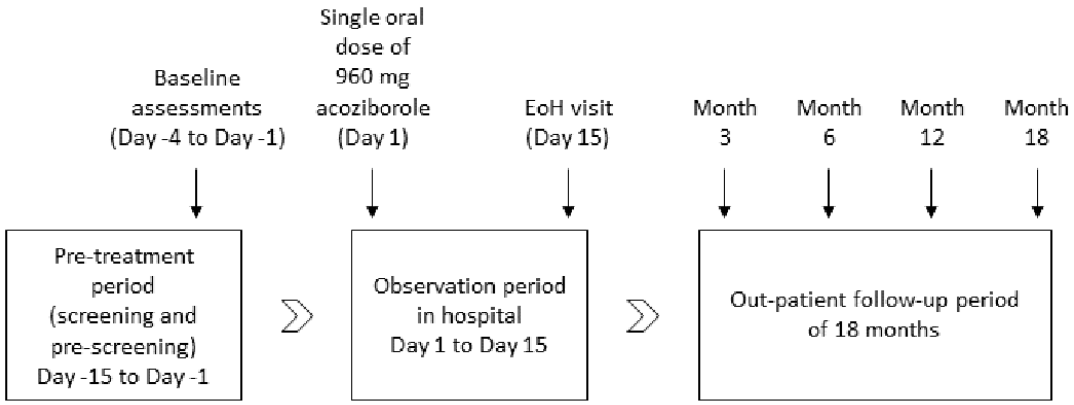
5.3.2.1. DNDi-OXA-02-HAT

5.3.2.1.1. Efficacy and safety study of acoziborole (SCYX-7158) in patients with human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense: a multicentre, open-label, prospective study

5.3.2.1.2. Study design

DNDi-OXA-02-HAT was a single-arm, open-label, single pivotal Phase 2/3 study to assess the efficacy and safety of a single oral dose of acoziborole administered in a fasting state to adults and adolescents (≥15 years old) with parasitologically-confirmed g-HAT (all stages).

Figure 20. Study schema



EoH = End-of-hospitalization.

Treatment

Single oral dose of 960 mg of acoziborole (3 x 320-mg tablets, batch number PD15019) administered under overnight fasting conditions on Day 1.

Patient population

Centres were located in the DRC (12 centres) and Guinea (1 main centre and 2 satellite centres for follow-up). Participants were mainly recruited at hospital when consulting for symptoms (passive screening), but also by mobile medical teams working in the field (active screening).

Investigation of potential infection during screening was first performed by assessing clinical signs, including the presence of swollen cervical lymph nodes, and by serological screening tests (rapid diagnostic test or card agglutination test for trypanosomiasis [CATT]).

Confirmed diagnosis of g-HAT and baseline disease staging thereafter required further assessment according to multiple criteria:

Table 9. Eligibility criteriastudy DNDi-OXA-02-HAT

Inclusion criteria (all)	Exclusion criteria (any)
Ability to ingest oral tablets	Severe malnourishment (BMI <16 kg/m²)
≥15 years old	Pregnancy or breastfeeding
Karnofsky index >50	Current alcohol abuse or drug addiction
Having a permanent address or being traceable by other persons, willing and able to comply with follow-up visits	Clinically significant medical conditions other than g-HAT that could, in the opinion of the Investigator, jeopardize the participant safety or interfere with participation in the study (eg, significant liver or cardiovascular disease, suspected or proven active infection, CNS trauma or seizure, coma or consciousness disturbances)
Agreement to be hospitalized for a minimum of 15 days and to receive the study treatment (ie, signed informed consent).	
	Severely deteriorated health status (eg, cardiovascular shock, respiratory distress syndrome, or end-stage disease)
<u>For participants with late-stage g-HAT</u>:	Participants previously enrolled in the study or have already received treatment for HAT (except pentamidine)
- Confirmation of g-HAT by detection of the parasite in the blood and/or the lymph and/or the CSF, at the investigational centre	Foreseeable difficulty complying with follow-up, including migrant worker, refugee status, itinerant trader
- If no parasite in CSF, the CSF WBC count had to be >20 cells/µL of CSF	Not tested for malaria and/or not having received appropriate treatment for malaria or soil-transmitted helminthiasis
<u>For participants with early- or intermediate-stage g-HAT</u>:	Clinically significant abnormal laboratory values including:
- Confirmation of g-HAT by detection of the parasite in the blood and/or the lymph at the investigational centre	- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2 x ULN;
- Absence of parasites in the CSF	- Total bilirubin >1.5 x ULN;
- CSF WBC of 6-20 cells/µL of CSF for intermediate stage or ≤5 cells/µL of CSF for early stage	- Severe leukopenia at less than 2000/mm³;
	- Potassium <3.5 mmol/L;
	- Any other clinically significant abnormal laboratory value.

Abbreviations: **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **BMI**, body mass index; **CNS**, central nervous system; **CSR**, clinical study report; **CSF**, cerebrospinal fluid; **g-HAT**, human African trypanosomiasis due to *Trypanosoma brucei gambiense*; **ULN**, upper limit of normal; **WBC**, white blood cells.

Karnofsky index

The Karnofsky Performance Scale (KPS) is a standardised tool used to assess a patient's functional status on an 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death), particularly in those with chronic or terminal illnesses. A score of 50 is described as "*the patient requires considerable assistance and frequent medical care*".

Prevention of pregnancy during study treatment

Women, as well as men, of reproductive age were advised to have protected sexual relations during the observation period and up to the Month 3 visit. Contraceptive methods, i.e., hormonal contraception and/or condoms, were available to patients free of charge throughout the duration of their participation in the study.

Detection of trypanosomes in lymph and blood

Local microscopic examination of fresh lymph node aspirate collected by needle biopsy (if swollen lymph nodes were present) and in blood, using the Woo test (capillary tube centrifugation; CTC) or the mini-anion exchange centrifugation test (mAECT)[7]. An improved technique, the mAECT on buffy coats[8], was used whenever possible in participants with positive serological tests and negative findings in the usual parasitological tests. Short digital videos of the parasitological tests were taken to ensure the quality of the diagnosis and prevent the risk of erroneous inclusion of participants in the study.

Detection of trypanosomes in CSF

Lumbar puncture for disease staging was performed only at the investigational centres. Parasitological tests were performed locally after modified single centrifugation of the CSF. Only patients in whom the presence of parasites was confirmed by at least two team members at the investigational centre and approved by the Investigator, were included in the study, regardless of the findings reported by the mobile teams. Parasitological and WBC counting techniques were performed according to adapted WHO recommendations[9]. Short digital videos of the parasites as well as pictures of WBC counting in CSF were taken to ensure the quality of the diagnosis and the assessment of the success rate.

Clinical examinations

Clinical physical and neuropsychiatric examinations were performed locally.

Classification of stage/severity

Table 10. Classification of stage/severity subgroups at study entry

Trypanosomes in CSF	WBCs in CSF		
	≤5 cells/µL	6-20 cells/µL	>20 cells/µL
Trypanosomes in CSF (positive)	Late-stage (subgroup C)	Late-stage (subgroup D)	Late-stage (subgroup E)
No trypanosomes in CSF (negative)	Early-stage (subgroup A)	Intermediate-stage (subgroup B)	Late-stage (subgroup F)

CSF = Cerebrospinal fluid; WBC = White blood cell count.

[7] Büscher P, Mumba Ngoyi D, Kaboré J, Lejon V, Robays J, Jamonneau V, et al. Improved Models of Mini Anion Exchange Centrifugation Technique (mAECT) and Modified Single Centrifugation (MSC) for Sleeping Sickness Diagnosis and Staging. PloS Negl Trop Dis. 2009;3(11):e471.
[8] Camara M, Camara O, Ilboudo H, Sakande H, Kaboré J, N'Dri L, et al. Sleeping sickness diagnosis: use of buffy coats improves the sensitivity of the mini anion exchange centrifugation test. Trop Med Int Health. 2010;15(7):796-9.
[9] WHO (2007). Recommendations of the Informal Consultation on Issues for Clinical Product Development for Human African Trypanosomiasis. World Health Organization. WHO/CDS/NTD/IDM/2007.1

5.3.2.1.3. Objectives and estimands

Primary objective

To estimate the treatment success rate at 18 months of follow-up with acoziborole, administered as a single 960 mg oral dose to patients in the fasting state with late-stage g-HAT.

Estimand for the primary objective

The estimand framework was not applied in this study.

Primary efficacy endpoint

Outcome (success or failure) at the 18 months visit according to the adapted WHO criteria, defined as:

Success:

- cure (participant alive, no evidence of parasites in any body fluids, and CSF WBC ≤20 cells/µL at M18 or later with non-haemorrhagic lumbar puncture), or
- probable cure (ie, participant without lumbar puncture at M18 but with CSF WBC ≤20 cells/µL at M12 or CSF WBC ≤50 cells/µL at M6, and no clinical signs or symptoms at M18);

***Failure*:**

- relapse (evidence of trypanosomes in any body fluid within 18 months),
- probable relapse (participant with a non-haemorrhagic lumbar puncture but CSF WBC >20 cells/µL at M18),
- death for any reason (within 18 months),
- use of rescue medication (within 18 months),
- loss to follow-up for any reason (within 18 months),
- refusal of all post-treatment lumbar puncture (within 18 months), and,
- in the absence of lumbar puncture at the M18 visit, an unfavourable outcome earlier than M18 (CSF WBC >50 cells/µL at M6 or >20 cells/µL at M12 or after M18), or signs and symptoms evoking a relapse at M18

Statistical methods for estimation and sensitivity analysis on primary endpoint

Statistical methods were planned in the protocol and were then updated, clarified, agreed, and approved in the final SAP, Version 4.0, dated 17 Mar 2021.

Two cohorts of patients were studied: patients with early- or intermediate-stage HAT and patients with late-stage HAT. For the analysis, HAT stages were determined according to criteria described in the SAP.

<u>Analysis Sets</u>

Analysis sets were clarified in the SAP relative to the protocol and are presented per SAP below. The mITT set was used for primary efficacy analyses.

Set of screened HAT-positive patients: all HAT-positive patients who signed the informed consent.

Treated set: all patients who received at least one tablet of acoziborole.

Modified intention-to-treat (mITT) set: all patients who received at least one tablet of acoziborole, excluding patients who fled the region due to armed conflict or natural disaster or due to force majeure and for whom no failure was detected early, and no data were available at Month 12 and Month 18.

Evaluable patients (EP) set: all mITT set patients, excluding:
• Patients lost to follow-up at 18 months (for primary efficacy endpoint and secondary efficacy outcome at Month 18), patients lost to follow-up at 12 months (for secondary efficacy outcome at Month 12), patients lost to follow-up at 6 months (for secondary efficacy outcome at Month 6), except those who were a failure before being lost to follow-up;
• Patients with no post-treatment lumbar puncture (i.e., patients who refused all lumbar puncture after treatment and who were not a failure);
• Patients who died for reasons clearly unrelated to efficacy or safety or disease evolution (those patients were reviewed during data review meeting);
• Early consent withdrawal (before Month 6, i.e., no planned visit attended after the Month 3 visit).

Per protocol (PP) set: all mITT set patients with no major protocol deviations. Major deviations were described by patient, and exclusion was decided during data review.

Main analysis methods for primary and important secondary endpoints

The primary analysis was the estimation of the success rate after 18 months of follow-up with acoziborole. An estimate of the success rate at Month 18 and the 95% Jeffreys CI of the estimate were provided. No formal hypothesis test was performed. The primary analysis was performed on late-stage patients included in the mITT set.

Success was defined as a cure or a probable cure. Failure was defined as a relapse, probable relapse, death for any reason (up to and including the Month 18 visit), use of rescue medication (up to and including the Month 18 visit), loss to follow-up for any reason (up to and including the Month 18 visit), refusal of all post-treatment lumbar puncture (up to and including the Month 18 visit), and, in the absence of lumbar puncture at the Month 18 visit, an unfavourable outcome earlier than Month 18, or signs and symptoms evoking a relapse at Month 18.

The success rate at Month 12 and Month 6 in late-stage patients was analysed as described for the primary endpoint (including sensitivity analyses).

The efficacy analysis for early- and intermediate-stage patients was a secondary analysis. It concerns the success rate at Month 18, Month 12, and Month 6 in early- and intermediate-stage patients.

The overall success rate at Month 18 (irrespective of the stage of HAT) was also calculated, along with the 95% Jeffreys CI.

Time to Proven and Definitive Failure in Late-Stage Patients was analysed using the Kaplan-Meier approach.

Handling of **missing data** is included in the derivation algorithms for outcome at Month 18, Month 12, and Month 6 for the primary and secondary efficacy endpoints related to outcome (success or failure). Different approaches to missing data handling were applied in the sensitivity analyses as specified in the table below.

The handling of post-treatment **intercurrent events** such as rescue medication intake, death, early consent withdrawal, lumbar puncture refusal, study discontinuation including war and natural disaster were considered in the algorithm for determining the outcome and in population definitions.

Sensitivity analyses

The analysis described for the primary analysis was repeated for late-stage patients included in the PP set, the EP set, and the Treated set. Furthermore, the analysis described for the primary analysis was performed on late-stage patients included in the mITT set with the "fair case", "best case" and "observed case" imputation methods.

Table 11. Methods of imputation for missing data for the primary efficacy endpoint

Imputation method	Rules of imputation
"Fair case" method	Responses of the following participants were replaced using a resampling approach: - Participants lost to follow-up (before or at M18, M12, and M6, respectively) - Participants who refused all post-treatment lumbar punctures - Participants without WBC in CSF data at the corresponding visit and no proven success according to prior or subsequent visit(s) The resampling was performed with a hot deck multiple imputation method as follows: - Responses were selected by simple random sampling (with replacement) among non-missing responses - The initial seed for random number generation used to select donor units was set to 495 - The imputation was repeated 100 times to produce 100 samples - For each sample, the estimate, its 95% Jeffrey CI and corresponding standard error (SE) was computed - The results of each of these analyses (estimates and SE) were combined using Rubin's rules to provide combined estimate and the 95% Jeffrey CI
"Best case" method	The following participants were considered to have treatment success: - Participants lost to follow-up (before or at M18, M12, and M6, respectively) - Participants who refused all post-treatment lumbar punctures
"Observed case" method	The following participants were considered as having a missing outcome: - Participants with missing data at M18, M12, and M6, respectively

Abbreviations: **CI**, confidence interval; **CSF**, cerebrospinal fluid; **CSR**, clinical study report; **M**, month; **SE**, standard error; **WBC**, white blood cells.

Standard of care as a yardstick for the Primary Efficacy Variable

As specified in the protocol, the current standard of care for late-stage patients is NECT, and the success rate with NECT was used as a yardstick. The success rates were provided study-by-study along with the 95% Jeffreys CI. The results were presented together in graphic format using a forest plot. Additionally, for illustrative purposes only, the historical success rate with fexinidazole was added to this forest plot.

Multiplicity

No adjustment for multiplicity was made. All confidence intervals were 95% two sided.

Secondary objectives

- To estimate the **treatment success** rate at 6 and 12 months in patients with late-stage g-HAT;
- To estimate the time course of the **failure rate** in patients with late-stage g-HAT;

• To assess the **safety profile** of a single dose of acoziborole in patients with g-HAT using historical data on NECT as a yardstick;

• To estimate the **treatment success** rate and the **safety profile** of acoziborole in early- or intermediate-stage g-HAT, using historical data on pentamidine as a yardstick;

• To establish the **relationship** between acoziborole PK (blood and CSF) and efficacy.

Estimands for the secondary objectives

The estimand framework was not applied in this study.

Secondary efficacy endpoints

• Response (success or failure) at Month 12 in patients with late-stage HAT;

• Response (success or failure) at Month 6 in patients with late-stage HAT;

• Response (success or failure) at Month 18 in patients with early- and intermediate-stage HAT (specific algorithm for success determination);

• Response (success or failure) at Month 12 in patients with early- and intermediate-stage HAT (specific algorithm for success determination);

• Response (success or failure) at Month 6 in patients with early- and intermediate-stage HAT (specific algorithm for success determination);

- The algorithms for outcomes at M6, M12 and M18 in late- and early- or intermediate-stage g-HAT, respectively, differed and were defined in Section 10 of the SAP (version 4.0) and are not shown here.

- The same analyses as described above for the primary endpoint were conducted (including sensitivity and 'by-centre' analyses).

• Time to proven and definitive failure in patients with late-stage HAT.

- The time of failure was the time of the first objective evidence of sustainable failure defined as:

• Death for any reason (at any time on or after administration of acoziborole);

• Decision to use rescue medication (at any time on or after administration of acoziborole);

• Observation of trypanosomes in any body fluid at Month 6, Month 12, or Month 18;

• A CSF WBC >50 cells/µL at Month 6 followed by a confirmation of failure defined as some or all of the following:

o CSF WBC >20 cells/µL at Month 12;

o CSF WBC >20 cells/µL at Month 18;

o Signs and symptoms evoking a relapse at Month 12;

o Signs and symptoms evoking a relapse at Month 18;

- A CSF WBC >20 cells/µL at Month 12 followed by a confirmation of failure defined as one or both of the following:
    - CSF WBC >20 cells/µL at Month 18;
    - Signs and symptoms evoking a relapse at Month 18;
- A CSF WBC >20 cells/µL at Month 18.

Safety endpoints

See Clinical Safety, below.

Pharmacokinetic endpoints

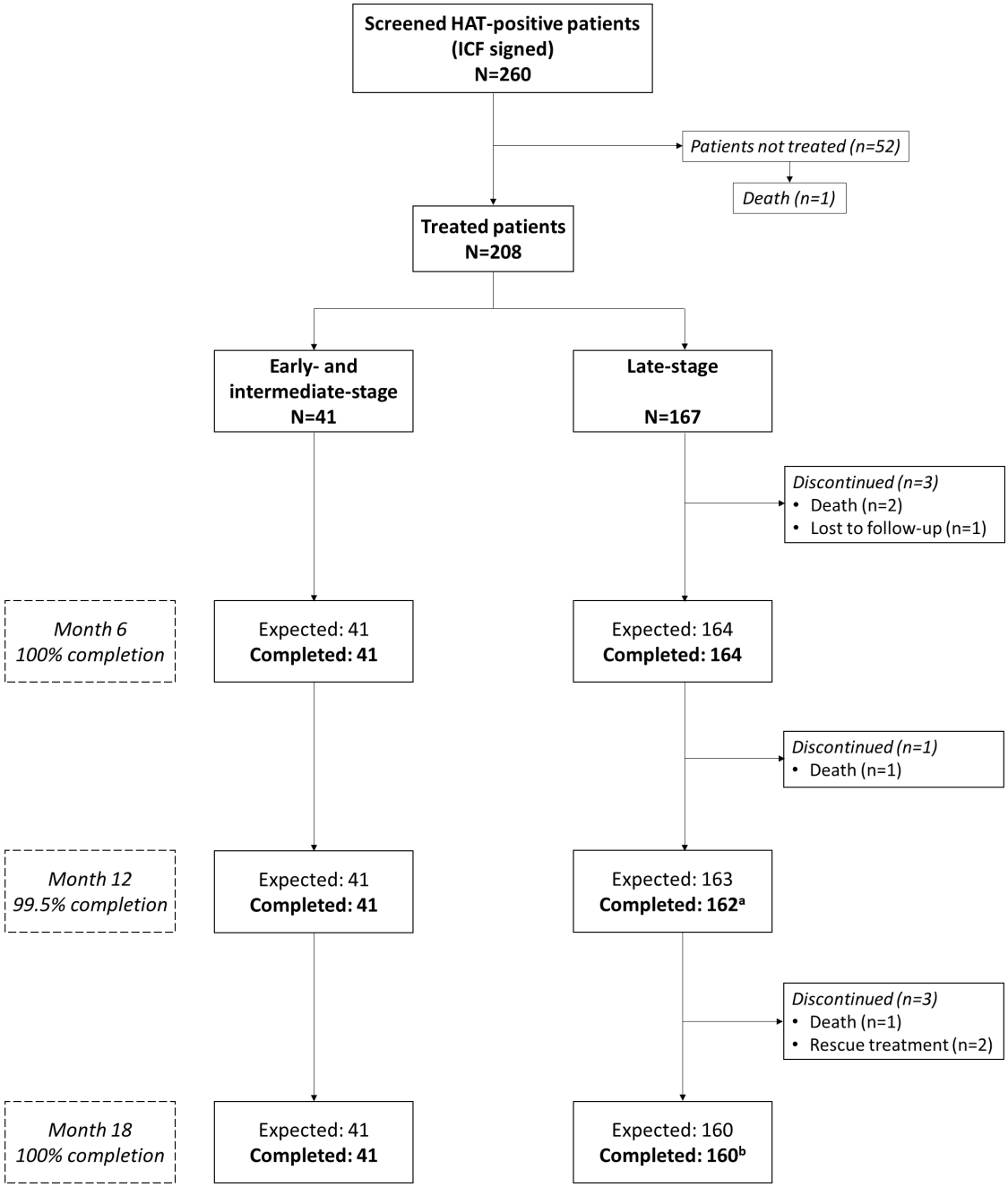
See Pharmacokinetics, above.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

All statistical methods are described above under *Statistical methods for estimation and sensitivity analysis on primary estimand<s>*.

5.3.2.1.4. Results

Participant flow and numbers analysed



Of the 260 screened HAT-positive patients who signed the informed consent form (ICF), 208 patients received the study drug and the remaining 52 patients were not treated, including 1 patient who died during screening. The reason for screening failure was missing for 7 patients. general baseline demographics were not notably imbalanced between screening successes and failures.

Table 12.Excluded participants who did not meet inclusion criteria and/or met exclusion criteria – (DNDi-OXA-02-HAT)

Category Inclusion criteria unmet/Exclusion criteria met	n (%) [a]
Screening failures	**45 (100.0%)**
Ineligible due to inclusion criteria unmet	**36 (80.0%)**
Diagnosis of g-HAT confirmed as stated in the protocol	35 (77.8%)
15 years of age or older	1 (2.2%)
Karnofsky Performance Status above 50	1 (2.2%)
Ineligible due to exclusion criteria fulfillment	**27 (60.0%)**
Not having received appropriate treatment for soil-transmitted helminthiasis	18 (40.0%)
Clinically significant abnormal laboratory value including: AST and/or ALT > 2 ULN, total bilirubin > 1.5 ULN, or severe leukopenia (< 2000/mm^3), or potassium < 3.5 mmol/L	14 (31.1%)
Any other clinically significant abnormal laboratory value	12 (26.7%)
Not tested for malaria and/or not having received appropriate treatment for malaria	8 (17.8%)
Clinically significant medical condition that could, in the opinion of the Investigator, jeopardize the participants' safety or interfere with participation in the study	5 (11.1%)
Current alcohol abuse or drug addiction	1 (2.2%)
Pregnancy or breastfeeding (for female participants)	1 (2.2%)
Severely deteriorated health status, e.g., due to cardiovascular shock, respiratory distress syndrome or end-stage disease	1 (2.2%)

Sources: Table produced using SAS 9.4 and DNDi-OXA-02-HAT raw data from SDTM/ADAM database exports

Abbreviations: **AST**, aspartate aminotransferase; **ALT**, alanine aminotransferase; **g-HAT**, human African trypanosomiasis due to *Trypanosoma brucei gambiense*; **ULN,** upper limit of normal

a n (%) = number (percentage) of participants with at least one inclusion/exclusion criterion failure

Participants may present more than one failure to the eligibility criteria and can therefore be counted in more than one criterion and category. As a result, (i) the sum of category-specific n values exceeds the total number of affected participants (N = 45), and (ii) within a given category, the sum of n across eligibility criteria exceeds the total number of affected participants in that category.

Deviations from study plan

There were 3 protocol amendments during the study (2 substantial and 1 non-substantial) since the initial protocol (Version 1.0) dated 27 Apr 2016. The most substantial changes (non-exhaustive) are summarised below:

Amendment Number	Protocol Version	Release Date	Purpose of Amendment
1	2.0	17 Dec 2018 (study ongoing)	Change in sample size Addition of clarification concerning finalization of the SAP
2	3.0	07 Jan 2020 (study ongoing)	Deletion of the surrogate endpoint at Month 12 for late-stage patients Efficacy analysis at Month 12 in late-stage patients became a secondary endpoint

3	4.0	11 Aug 2020 (study ongoing)	*No substantial changes*

Overall, 173 patients (83.2%) had a minor protocol deviation as per the definition of the per protocol analysis and no patient had a major protocol deviation. From a GCP point of view, some of them were considered as major and a corrective and preventive action plan was put in place. The categories concerned included performance of procedures (lumbar puncture, haematology and urine pregnancy test) prior to informed consent, missing screening urine pregnancy tests, and late reporting of 2 SAEs (1 pregnancy and 1 death of a baby). There was a high rate of procedures outside allocated time frame (56.6% participants affected) and missed procedures (40.5% participants affected).

Baseline data

Demographics

Table 13.Baseline demographic characteristics of study participants - mITT set

Characteristics	Early and Intermediate stage (N = 41)	Late stage (N = 167)	Total (N = 208)
Sex (M/F) n (%)	15/26 (36.6/63.4)	102/65 (61.1/38.9)	117/91 (56.3/43.8)
Age (years)			
Mean (±SD) [range]	40.9±15.0 [17.0, 68.0]	32.4±11.2 [15.0, 59.0]	34.0±12.4 [15.0, 68.0]
Median (Q1, Q3)	40.0 (29.0, 52.0)	30.9 (23.0, 40.0)	31.3 (24.0, 43.0)
BMI (kg/m²)			
Mean (SD) [range]	20.2±2.7 [16.4, 29.7]	20.0±2.6 [15.2, 28.8]	20.0±2.6 [15.2, 29.7]
Median (Q1, Q3)	20.0 (18.4, 21.2)	19.8 (17.9, 22.0)	19.8 (18.0, 21.9)
Country n (%)			
DRC	34 (82.9)	140 (83.8)	174 (83.7)
Guinea	7 (17.1)	27 (16.2)	34 (16.3)

Abbreviations: **BMI**, body mass index; **CSR**, clinical study report; **DRC**, Democratic Republic of Congo; **F**, female; **M**, male; **mITT**, modified intention-to-treat; **Q**, quartile; **SD**, standard deviation.

Staging of g-HAT

Table 14. Examination results of CSF samples for g-HAT diagnosis - mITT set

Description	Early and Intermediate stage (N = 41)	Late stage (N = 167)	Total (N = 208)
Trypanosomes in CSF			
Positive, n (%)	0 (0)	139 (83.2)	139 (66.8)
Negative, n (%)	41 (100)	28 (16.8)	69 (33.2)
WBC/µL of CSF			
Mean (±SD)	7.8±5.3	398.8±438.4	321.3±422.3
Median (min-max)	6.0 (1.0-20.0)	260.0 (6.0-2705)	190.0 (1.0-2705)
CSF WBC categories, n (%)			
≤5 cells/µL	18 (43.9)	0 (0)	18 (8.7)
[5-20] cells/µL	23 (56.1)	6 (3.6)	29 (13.9)

Description	Early and Intermediate stage (N = 41)	Late stage (N = 167)	Total (N = 208)
[20-100] cells/µL	0 (0)	33 (19.8)	33 (15.9)
>100 cells/µL	0 (0)	128 (76.6)	128 (61.5)

Abbreviations: **CSF**, cerebrospinal fluid; **CSR**, clinical study report; **g-HAT**, human African trypanosomiasis due to *Trypanosoma brucei gambiense*; **mITT**, modified intention-to-treat; **SD**, standard deviation; **WBC**, white blood cells.

a One participant had missing WBC in CSF at baseline and was considered as having WBC in CSF >100 cells/µL.

Clinical signs and symptoms of g-HAT

In general, clinical signs and symptoms of HAT at baseline were more frequently reported in the late-stage HAT cohort compared to the early- and intermediate-stage HAT cohort. Gait disturbances, speech disturbances and convulsions were *only* reported in the late-stage HAT cohort.

The clinical signs and symptoms of HAT that were reported in the early- and intermediate-stage HAT cohort at baseline had the following prevalence:

- >50% of patients: headache (56.1%);
- 5-50% of patients: fever (43.9%), asthenia (26.8%), pruritus (26.8%), insomnia (24.4%), weight loss (24.4%), other (17.1%), drowsiness (14.6%), nausea (14.6%), sexual impotence (13.3%; men only), anorexia (9.8%);
- <5% of patients: diarrhoea (4.9%), amenorrhea (3.8%; women only), behavioural disturbances (2.4%), tremor (2.4%).

The clinical signs and symptoms of HAT that were reported in the late-stage HAT cohort at baseline had the following prevalence:

- >50% of patients: drowsiness (74.3%), headache (64.1%), asthenia (57.5%), pruritus (57.5%);
- 5-50% of patients: amenorrhea (47.7%; women only), fever (44.9%), insomnia (40.1%), weight loss (40.1%), tremor (39.5%), sexual impotence (34.7%; men only), other (31.7%), gait disturbances (28.1%), behavioural disturbances (21.0%), anorexia (18.0%), speech disturbances (16.8%), nausea (8.4%);
- <5% of patients: convulsions (3.0%), diarrhoea (1.8%).

Over half of all patients (55.3%) presented with swollen cervical lymph nodes: 48.8% of patients with early- or intermediate-stage HAT and 56.9% of patients with late-stage HAT.

Psychiatric examination was normal in all participants with early- and intermediate-stage HAT.

The most frequently observed abnormalities in the late-stage HAT cohort were mild to moderate behavioural disturbances (in 19.8% of patients), reduced verbal flow (17.4%), lethargy (in 17.4% of patients), psychomotor slowing (16.8%), impaired memory (12.6%), dysarthria (11.4%), exaggerated verbal flow (7.2%) and depressed mood (6.0%). In patients with late-stage HAT, 25.7% of patients had difficulties with or required help walking and 22.2% of patients were reported with mild to moderate involuntary movements.

Assessments of motor coordination revealed the presence of tremor in 30.8% of patients overall (7.3% of patients with early- or intermediate-stage HAT and 36.5% of patients with late-stage HAT), impaired balance (Romberg test) in 15.4% of patients overall (0.0% and 19.2% of patients, respectively), and disruption of rapid alternating movements in 13.9% of patients overall (2.4% and 16.8% of patients,

respectively). The presence of the palm-chin reflex was reported in 21.6% of patients overall (2.4% of patients with early- or intermediate-stage HAT and 26.3% of patients with late-stage HAT).

Severity of disease

Table 15. Analysis subgroups - (mITT set)

	Total N=208
Among patients included in the mITT:	
HAT Stage	
Stage 1 [n (%)]	18 (8.7)
Intermediate stage [n (%)]	23 (11.1)
Stage 1 and intermediate stage [n (%)]	41 (19.7)
Stage 2 [n (%)]	167 (80.3)
HAT Subgroup	
Subgroup A: trypanosomes in CSF negative and WBC in CSF <= 5/µl [n (%)]	18 (8.7)
Subgroup B: trypanosomes in CSF negative and WBC in CSF [6-20/µl] [n (%)]	23 (11.1)
Subgroup C: trypanosomes in CSF positive and WBC in CSF <= 5 /µl [n (%)]	0 (0.0)
Subgroup D: trypanosomes in CSF positive and WBC in CSF [6-20/µl] [n (%)]	6 (2.9)
Subgroup E: trypanosomes in CSF positive and WBC in CSF > 20/ µl [n (%)]	133 (63.9)
Subgroup F: trypanosomes in CSF negative and WBC in CSF > 20/µl [n (%)]	28 (13.5)
missing	0

Medical history

Table 16. Medical history: PTs reported in ≥5% of patients in either cohort (mITT set)

SOC PT	Early- and Intermediate-Stage (N = 41)			Late-Stage (N = 167)			Total (N = 208)		
	n	%	MH events	n	%	MH events	n	%	MH events
Any medical history	**34**	**82.9**	**83**	**127**	**76.0**	**329**	**161**	**77.4**	**412**
Infections and infestations	**20**	**48.8**	**22**	**62**	**37.1**	**80**	**82**	**39.4**	**102**
Malaria	15	36.6	15	39	23.4	39	54	26.0	54
Investigations	**14**	**34.1**	**20**	**63**	**37.7**	**86**	**77**	**37.0**	**106**
Electrocardiogram T wave inversion	2	4.9	2	30	18.0	30	32	15.4	32
Electrocardiogram T wave amplitude decreased	2	4.9	2	15	9.0	17	17	8.2	19
Blood albumin decreased	5	12.2	5	9	5.4	9	14	6.7	14
Cardiac disorders	**9**	**22.0**	**12**	**39**	**23.4**	**49**	**48**	**23.1**	**61**
Atrioventricular block first degree	5	12.2	5	13	7.8	13	18	8.7	18
Sinus bradycardia	1	2.4	1	10	6.0	10	11	5.3	11
Blood and lymphatic system disorders	**3**	**7.3**	**3**	**22**	**13.2**	**23**	**25**	**12.0**	**26**
Anaemia	2	4.9	2	21	12.6	22	23	11.1	24
Gastrointestinal disorders	**7**	**17.1**	**8**	**12**	**7.2**	**14**	**19**	**9.1**	**22**
Gastritis	3	7.3	3	5	3.0	5	8	3.8	8
Social circumstances	**5**	**12.2**	**5**	**11**	**6.6**	**12**	**16**	**7.7**	**17**
Menopause	5	12.2	5	9	5.4	9	14	6.7	14
Vascular disorders	**4**	**9.8**	**4**	**4**	**2.4**	**4**	**8**	**3.8**	**8**
Hypertension	3	7.3	3	4	2.4	4	7	3.4	7

MH = Medical history; mITT = Modified intention-to-treat; PT = Preferred term; SOC = System organ class.

Prior medications

All participants had to be treated for soil-transmitted helminthiasis to be eligible for inclusion in the study, therefore all (100% [208/208]) participants received benzimidazole derivatives before the study start: 89.4% (186/208) received albendazole and 10.6% (22/208) received mebendazole. One participant (0.5%) in the late-stage g-HAT cohort received ivermectin in addition to a benzimidazole derivative. Treatment was to be followed by a recovery period of at least 3 days between the last dose of the antihelminth agent and the administration of acoziborole.

All participants with a positive test for malaria (using blood slide and/or rapid diagnostic test) also had to receive treatment with artemether and lumefantrine (unless contraindicated) before the study start. Overall, 26.4% (55/208) of included participants received artemether/lumefantrine therapy. All of the existing artemisinin-based combination therapies used against malaria have effects on the QT interval (QT). Coartem was chosen because its effects on QT prolongation are known to be moderate and well quantified. Treatment was to be followed by a recovery period of at least 3 days between the last dose of the antimalarial agent and the administration of acoziborole.

Other frequently used prior therapies included paracetamol (55.8% [116/208]) and diclofenac (7.7% [16/208]). These treatments were provided to treat pain or headache associated with lumbar puncture when needed. All other prior drugs were taken by ≤5% of participants overall.

Concomitant medications

During the study up to M6 of follow up, 68.8% (143/208) of the participants took at least one concomitant medication. The most frequently used concomitant treatments (>5% of participants) were: paracetamol (57.2% [119/208]), diclofenac (13.9% [29/208]), artemether/lumefantrine, 13.5% [28/208]), chlorpromazine (6.7% [14/208]), promethazine (5.8% [12/208]), and amoxicillin (5.8% [12/208]).

Exposure

All participants (100% [208/208]) received the full 960 mg oral dose of acoziborole (3 × 320 mg tablets).

Outcomes and estimation

Primary efficacy analysis with sensitivity analyses

Table 17. Success rate at M18 in participants with late-stage g-HAT – primary and sensitivity analyses

Description	Success N (%) [95% CI]	Failure N (%) [95% CI]
Primary analysis: mITT set[a] (N = 167)	159 (95.2%) [91.2-97.7]%	8 (4.8%) [2.3-8.8]%
PP set (N = 167)	159 (95.2%) [91.2-97.7]%	8 (4.8%) [2.3-8.8]%
EP set (N = 162)	159 (98.1%) [95.1-99.5]%	3 (1.9%) [0.5-4.9]%
Treated set (N = 167)	159 (95.2%) [91.2-97.7]%	8 (4.8%) [2.3-8.8]%
mITT "fair case" method (N = 167)	ND[b]	ND[b]
mITT "best case" method (N = 167)	160 (95.8%) [91.9-98.1]%	7 (4.2%) [1.9-8.1]%
mITT "observed case" method (N = 165)	158 (95.8%) [91.9-98.1]%	7 (4.2%) [1.9-8.1]%

Abbreviations: **CI**, confidence interval; **CSR**, clinical study report; **EP**, evaluable participants; **g-HAT**, human African trypanosomiasis due to *Trypanosoma brucei gambiense*; **mITT**, modified intention-to-treat; **ND**, not done; **PP**, per protocol.

a No ITT set was formally defined in this study, but it would be identical to the mITT set since no participants were excluded from this set.

b As only 1 participant met the criteria for resampling using hot deck multiple imputation, the results using the "fair case" method would be identical to the primary analysis or the sensitivity analysis using the "best case" method.

Table 18. Reason for failure at 18 months – mITT set

Patient ID	Classification for failure
[redacted]	Positive for trypanosomes between drug intake and Month 18
	Positive for trypanosomes between drug intake and Month 18
	Positive for trypanosomes between drug intake and Month 18
	Death between drug intake and Month 6
	Death between drug intake and Month 6
	Death between Month 6 and Month 12
	Death between Month 12 and Month 18
	Lost to follow-up between drug intake and Month 6

ID = Identification; mITT = Modified intention-to-Treat.

Narratives were provided for deaths occurring between drug intake and primary endpoint. None of the cases of on-study offer death concrete evidence to support that death was the result of a lack of efficacy of acoziborole.

An exploratory dose-response analysis was performed using DBS and CSF acoziborole concentrations of three participants with confirmed treatment failure (considered relapse) in comparison with data from the whole study population (see Pharmacokinetics AR).

Secondary efficacy analyses

Treatment success rate at 6 and 12 months in patients with late-stage g-HAT

The success rate at Month 12 in late-stage HAT patients using the primary analysis (derivation algorithm) was 95.8% (95% CI: 91.9; 98.1). There were 7 patients (4.2%) considered as failures; all these patients were also failures at Month 18 (the additional failure at Month 18 was due to a patient who died between the Month 12 and Month 18 visits).

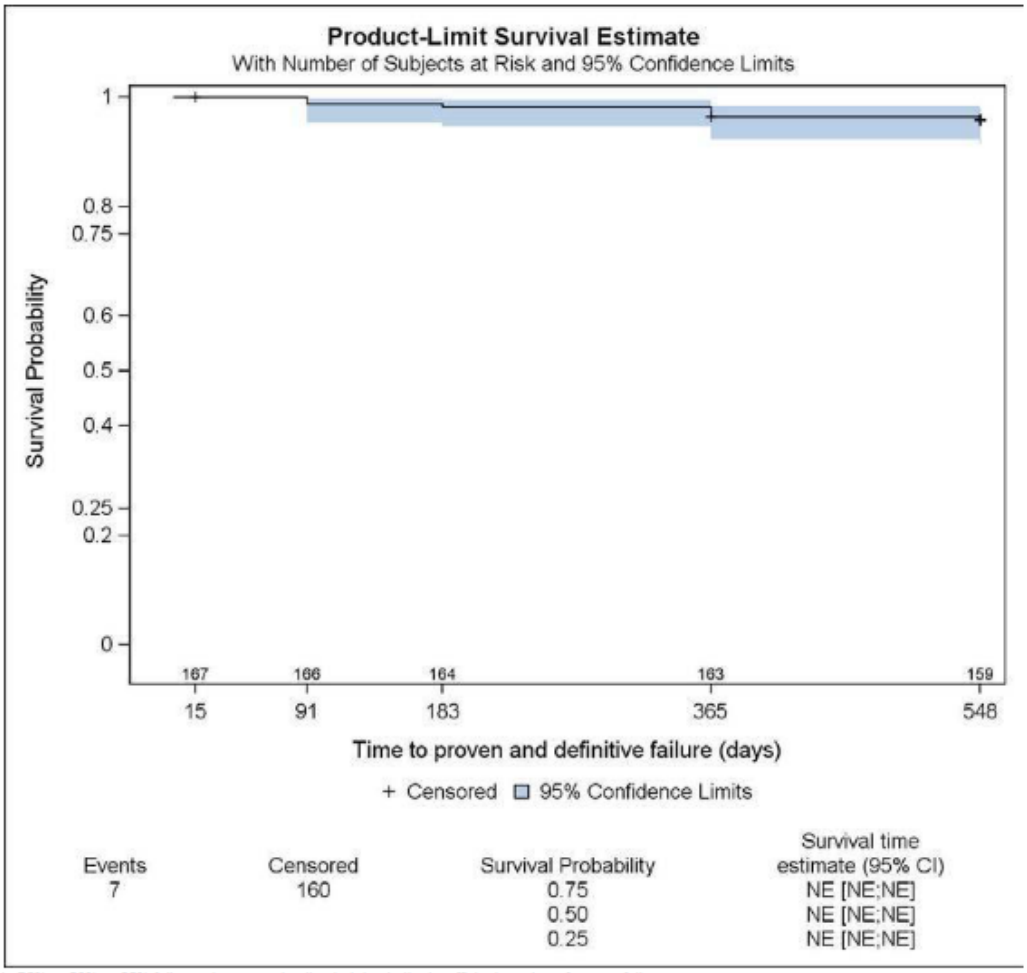
The success rate at Month 6 in the same cohort using the same analysis was 94.6% (95% CI: 90.4; 97.3). There were 9 patients (5.4%) considered as failures; of these 9 failures at M6, 3 patients became successes at M12 and again at M18. Conversely, 2 patients who were a success at Month 6 became a failure later in the study.

Treatment success rate in patients with early- or intermediate-stage g-HAT

The success rate at M6, M12 and M18 in patients with early- or intermediate-stage HAT was 100%.

Time to proven and definitive failure in patients with late-stage HAT

Figure 21. Kaplan-Meier analysis of time to proven and definitive failure in Patients with Stage 2 HAT (mITT)



Note: time to 75% or 50% or 25% failure rate were not estimated due to the insufficient number of proven failures.

Pre-defined and post-hoc subgroup analyses

Table 19. Descriptive analysis and trend test of success rates at 18 months: baseline severity subgroups A vs B vs C vs D vs E vs F (mITT)

	HAT Subgroup				
	A N=18	B N=23	F N=28	D N=6	E N=133
Success rate at 18 months					
non-missing	18	23	28	6	133
FAILURE [n (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (6.0)
95% Jeffreys CI	0.0 ; 12.9	0.0 ; 10.2	0.0 ; 8.5	0.0 ; 33.0	2.9 ; 11.0
SUCCESS [n (%)]	18 (100.0)	23 (100.0)	28 (100.0)	6 (100.0)	125 (94.0)
95% Jeffreys CI	87.1 ; 100.0	89.8 ; 100.0	91.5 ; 100.0	67.0 ; 100.0	89.0 ; 97.1
Cochran-Armitage test : = p=0.0595 A: Trypanosomes in CSF negative and WBC in CSF ≤ 5/µl (=stage 1) B: Trypanosomes in CSF negative and WBC in CSF [6-20/µl] (=intermediate stage) C: Trypanosomes in CSF positive and WBC in CSF ≤ 5/µl D: Trypanosomes in CSF positive and WBC in CSF [6-20/µl] E: Trypanosomes in CSF positive and WBC in CSF > 20/µl F: Trypanosomes in CSF negative and WBC in CSF > 20/µl					

Clinical studies in special populations

No dedicated clinical trials in special populations have been completed and presented as part of this submission.

The pivotal efficacy study DNDi-OXA-02-HAT excluded clinically significant medical conditions other than g-HAT, such as significant liver or renal disease. Pregnant women and paediatric patients <15 years of age were excluded from the study. There was no formal upper age limit for eligibility, but in practice the recruited study population was predominantly young adults (mean 34.0, median 31.3, Q1:Q3 24.0 to 43.0, min:max 15.0 to 68.0), with few patients over 65 years of age. Overall, 9 patients were adolescent (15 to 17 years old).

On-study treatment of concomitant malaria infection

As per local malaria treatment guidelines, assessment of cure was solely based on clinical outcomes, while only suspected failures would have to be tested for parasitology (Rapid Diagnostic Test (RDT/thick blood smear/thin blood smear).

Overall, 12 participants had more than one episode of malaria after acoziborole intake.

Table 20. Clinical outcome of malaria episodes occurring in study participants exposed to acoziborole, classified by time window and in chronological order (DNDi-OXA-02-HAT, DNDi-OXA-04-HAT)

Study	Participant ID	Dates of malaria treatment in study day [a]		Antimalarial drug	Clinical outcome
		Start Day	End Day		
Malaria medication completed up to 3 days before acoziborole intake					

Study	Participant ID	Dates of malaria treatment in study day [a]		Antimalarial drug	Clinical outcome
		Start Day	End Day		
DNDI-OXA-02-HAT		-18	-16	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-13	-11	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-11	-9	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-9	-7	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-9	-7	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-9	-7	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-8	-6	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-8	-6	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-8	-5	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-8	-6	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-7	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-7	-5	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-7	-5	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-7	-5	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-7	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-7	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-3	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-3	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered

Study	Participant ID	Dates of malaria treatment in study day [a]		Antimalarial drug	Clinical outcome
		Start Day	End Day		
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-3	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-3	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		-6	-4	Artemether/lumefantrine	Recovered
Malaria medication completed less than 3 days before acoziborole intake (no washout) and up to Day 7 after acoziborole intake					
DNDI-OXA-02-HAT		-4	-2	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		-1	2	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		1	3	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		2	4	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		2	4	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		3	5	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		3	5	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		3	5	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		3	6	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		3	5	Artemether	Recovered
DNDI-OXA-04-HAT		3	5	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		3	5	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		3	5	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		4	6	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		5	7	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		5	7	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		5	7	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		5	7	Artemether/lumefantrine	Recovered

Study	Participant ID	Dates of malaria treatment in study day [a]		Antimalarial drug	Clinical outcome
		Start Day	End Day		
Malaria medication received between Day 8 to Day 30 after acoziborole intake (period of strong CYP3A4 induction)					
DNDI-OXA-04-HAT		4	8	Artemether	Recovered
DNDI-OXA-02-HAT		8	10	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		9	10	Artesunate	Recovered
DNDI-OXA-02-HAT		11	13	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		15	17	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		16	18	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		22	24	Artemether/lumefantrine	Recovered
Malaria medication started ≥ 31 days after acoziborole intake					
DNDI-OXA-04-HAT		31	33	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		31	33	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		32	34	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		32	34	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		32	34	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		34	36	Artesunate	Recovered
DNDI-OXA-04-HAT		34	36	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		38	40	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		40	42	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		44	46	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		47	49	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		48	50	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		56	58	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		64	66	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		65	67	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		69	71	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		81	84	Artemether/lumefantrine	Recovered
Malaria medication started ≥ 85 days (3 months) after acoziborole intake (no induction of CYP3A4)					
DNDI-OXA-02-HAT		89	91	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		91	93	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		91	93	Artemether	Recovered
DNDI-OXA-04-HAT		92	94	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		92	94	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		96	98	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		96	98	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		102	104	Artemether/lumefantrine	Recovered

Study	Participant ID	Dates of malaria treatment in study day [a]		Antimalarial drug	Clinical outcome
		Start Day	End Day		
DNDI-OXA-04-HAT		118	120	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		124	126	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		125	127	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		126	128	Artemotil	Recovered
DNDI-OXA-02-HAT		135	137	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		183	185	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		133	135	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		142	145	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		142	144	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		143	145	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		145	147	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		148	150	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		149	151	Artemether/lumefantrine	Recovered
DNDI-OXA-04-HAT		150	152	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		160	162	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		165	167	Artemether	Recovered
DNDI-OXA-02-HAT		171	173	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		181	183	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		182	184	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		182	184	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		182	185	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		183	185	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		183	185	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		185	187	Artemether/lumefantrine	Recovered
DNDI-OXA-02-HAT		186	188	Artemether	Recovered
DNDI-OXA-02-HAT		189	191	Artemether/lumefantrine	Recovered

Source: DNDI-OXA-02-HAT CSR, listing 16.2.5.4 Prior therapies; and listing 16.2.5.5 Concomitants therapies; DNDI-OXA-04-HAT CSR, listing 16.2.4.4 Concomitant medications; Safety set and listing 16.2.4.3 Previous medications

Abbreviations: **ID**, identifier

a Relative to acoziborole administration

b Six participants in DNDi-OXA-02-HAT study () and one participant in DNDi-OXA-04-HAT study () reported ≥ 2 antimalarial treatments after acoziborole intake

5.3.3. Analysis performed across trials (pooled analyses and meta-analysis)

As agreed with CHMP following the scientific advice led in November 2015 (EMEA/H/SA/3173/1/2015/III), efficacy results with acoziborole were compared to historical data with other reference drugs for the treatment of g-HAT for contextualisation of the results.

Study-by-study success rates with NECT along with the 95% Jeffreys CI are provided in the table below:

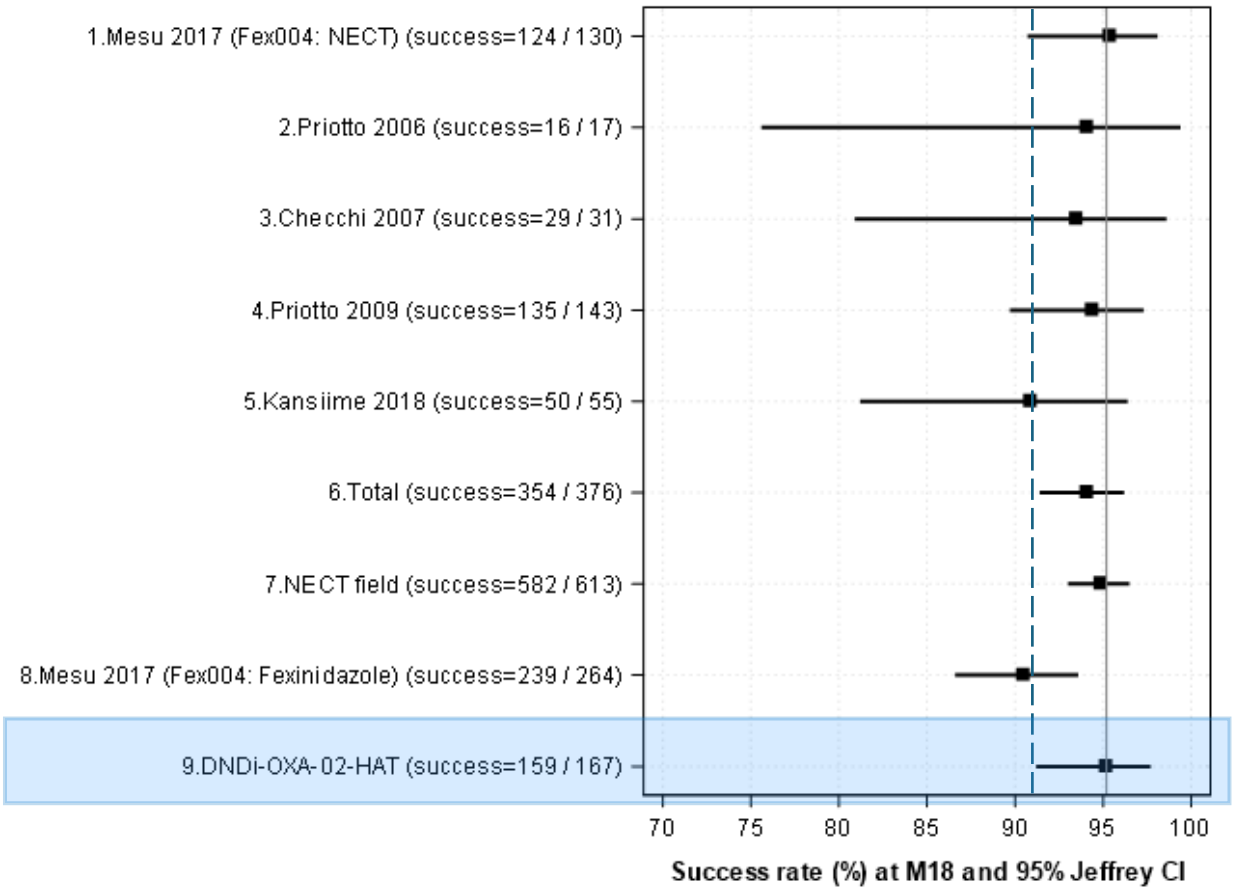
Table 21.Success rates at M18 with fexinidazole and NECT - Historical data[10]

Study	Success rate at 18 months for NECT ITT and 95% Jeffreys CI	Comments
Mesu 2018 [32] DND*i*FEX004 study [21]	Success rate: 124/130=95.4% 95% CI: 90.7%; 98.1%	Pivotal Fexinidazole study mITT: Success rate: 124/127 = 97.6% (RZD trial) 95% Jeffreys CI: 93.8%-99.3% Reason: 3 patients fleeing the region due to armed conflict
Priotto 2006 [33]	Success rate: 16/17=94.1% 95% CI: 75.6%; 99.4%	RZD trial
Checchi 2007 [34]	Success rate: 29/31=93.5% 95% CI: 80.9%; 98.6%	
Priotto 2009 [19]	Success rate: 135/143=94.4% 95% CI: 89.7%; 97.3%	Success rate: 138/143=96.5% 95% Jeffreys CI: 92.5%; 98.7% Note: exclusion of 3 deaths not related to treatment (RZD trial)
Kansiime 2018 [20]	Success rate: 50/55=90.9% 95% CI: 81.2%; 96.4%	RZD trial
NECT-Field [35]	Success rate: 582/613=94.9% 95% CI: 93.0%; 96.5%	Evaluations were not always done at Month 18 (one-arm field study with loose monitoring), 49 patients LTFU at Month 18 were not necessarily counted as failure
Total	**Success rate: 354/376=94.1% 95% CI: 91.4%; 96.2%**	**Overall success rate excluding NECT-field.**

CI = Confidence interval; ITT = Intention-to-treat; mITT = Modified intention-to-treat; LTFU = Lost to follow-up; NECT = Nifurtimox-eflornithine combination therapy; RZD = Randomized.

[10] Mesu VK, Kalonji WM, Bardonneau C, et al. Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. Lancet. 2018;391(10116):144-54.
Priotto G, Fogg C, Balasegaram M, et al. Three drug combinations for late-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Uganda. PLoS Clinical Trials. 2006;1(8):e39.
Checchi F, Piola P, Ayikoru H, Thomas F, Legros D, Priotto G. Nifurtimox plus eflornithine for late-stage sleeping sickness in Uganda: a case series. PLoS Negl Trop Dis. 2007;1(2):e64.
Priotto G, Kasparian S, Mutombo W, et al. Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. Lancet. 2009;374(9683):56-64.
Kansiime F, Adibaku S, Wamboga C, et al. A multicentre, randomised,non-inferiority clinical trial comparing a nifurtimox-eflornithine combination to standard eflornithine monotherapy for late stage *Trypanosoma brucei gambiense* human African trypanosomiasis in Uganda. Parasit Vectors. 2018;11(1):105.
Kuemmerle A, Schmid C, Bernhard S, et al. Effectiveness of Nifurtimox Eflornithine Combination Therapy (NECT) in *T. b. gambiense* Second Stage Sleeping Sickness Patients in the Democratic Republic of Congo: Report from a Field Study. PloS Negl Trop Dis. 2021;15(11):e0009903.

Figure 22. Success rate at M18 in participants with late-stage g-HAT treated with acoziborole - Comparison with yardsticksNECT and fexinidazole



1. to 5. Success rate at M18 in each reference study with NECT (ITT set), 6. Overall success rate at M18 from the 5 reference studies with NECT, 7. Success rate at M18 in the NECT-Field study, 8. Success rate at M18 in the reference study DNDiFEX004 with fexinidazole (ITT set), and 9. Success rate at M18 in study DNDi-OXA-02-HAT with acoziborole (mITT set).

Abbreviations: **CI**, confidence interval; **CSR**, clinical study report; **g-HAT**, human African trypanosomiasis due to *Trypanosoma brucei gambiense*; **ITT**, intention-to-treat; **M**, month; **mITT**, modified intention-to-treat; **NECT**, nifurtimox–eflornithine combination therapy.

5.3.4. Overall discussion and conclusions on clinical efficacy

5.3.4.1. Discussion

Dose selection

The dose was administered with the to-be-marketed formulation and was selected on the basis of the pre-clinical pharmacology package, aiming to provide an unbound CSF AUC0-24 of 5.81 µg/mL*h or more for at least 3 days.

The approach to dose selection was previously discussed and endorsed during CHMP Scientific Advice (EMEA/H/SA/3173/1/2015/III), although it was noted that CSF exposure levels at the 960 mg dose should be confirmed in the pivotal study. As the first post-dose lumbar puncture in study DNDi-OXA-02-HAT was performed on D11 after dosing (see Pharmacokinetics), the data generated do not allow for characterisation of the CSF PK profile during the first days of exposure, when it is most likely to predict clinical efficacy. However, the single-oral dose regimen of 960 mg has been administered to 208 participants with early-, intermediate- and late-stage parasitologically-confirmed g-HAT in pivotal efficacy and safety study DNDi-OXA-02-HAT and in 1206 participants with serologically positive non-parasitologically confirmed g-HAT in study DNDi-OXA-04-HAT, and

the high treatment success rates support the adequacy of the dose (see below).

Study design

The pivotal efficacy data supporting the claimed indication for acoziborole come from one pivotal phase 2/3 clinical study: study DNDi-OXA-02-HAT, a multicentre, open label, single-arm, clinical trial conducted in the DRC and Guinea.

This evaluated the efficacy and safety of a single dose (960 mg = 3 x 320 mg tablets administered in a fasting state) of acoziborole in adults and adolescents (≥15 years) with early-, intermediate- and late-stage parasitologically-confirmed g HAT.

The choice of an uncontrolled study design for the single pivotal study DNDi-OXA-02-HAT resulted from the substantial decline in g-HAT case incidence over the past 20 years, which prevented enrolling enough participants with T+ g-HAT within a reasonable time frame for the study. This rationale is understood and was previously discussed and agreed in CHMP Scientific Advice (EMEA/H/SA/3173/1/2015/III). Based on the maximum feasible enrolment in a reasonable timeframe of 2 years as agreed with the CHMP during Scientific Advice (EMEA/H/SA/3173/1/2015/III), it was initially planned to enrol a total of 210 evaluable participants with late-stage HAT. During a follow up Scientific Advice (EMEA/H/SA/3173/1/FU/1/2018/II), it was agreed to reduce the planned recruitment to enrol a total of 155 evaluable participants with late-stage HAT, despite the fact the study was already ongoing. This was justified on the basis that HAT is becoming increasingly rare due to the successful progress made in the control of the disease.

As untreated late-stage g-HAT is considered an invariably chronic disease, with the occurrence of spontaneous parasite clearance close to zero amongst patients in whom the diagnosis is confirmed with parasites in the CSF, it is considered possible to infer absolute efficacy of the study treatment in late-stage HAT (i.e. over putative placebo) even in the absence of a placebo arm, assuming a reasonable precision of the point estimate. The probability of confusing relapse/treatment failure of late-stage disease with reinfection during the 18-month follow-up period of the study is considered negligible as the estimated duration of the early stage of the disease, including following reinfection, is from 1.5 to 2 years.

The countries where the study was conducted, the DRC and Guinea, were the areas with the highest incidence of g HAT reported cases at the time of study initiation, but the results are considered generalisable to other endemic countries where g-HAT elimination remains a public health problem.

Selection of participants started with investigation of potential cases of infection, using clinical examination and rapid serological diagnostic tests. Confirmed diagnosis of g-HAT and baseline disease staging thereafter required further assessment (including lumbar puncture at the investigational centre) to address multiple criteria, including identification of parasites in blood, lymph ± CSF, which aligns with the WHO guidelines and eligibility criteria used in previous studies of g-HAT. Baseline disease severity was categorised according to the presence of parasites in CSF and the CSF WBC. The inclusion/exclusion criteria were appropriate and the approach to diagnostic investigation was sufficiently standardised.

All participants had to be treated for soil-transmitted helminthiasis (albendazole or mebendazole) and, where blood slide and/or rapid diagnostic test was positive, for malaria (artemether and lumefantrine, unless contraindicated) before the study start, followed by a recovery period of at least 3 days between the last dose of this treatment and the administration of acoziborole.

On-study dose was to re-administered if vomiting occurred within 15 minutes of administration. In practice, this did not occur in any study participant. Vomiting on Day 1 was recorded for 5 study participants, none of which required re-administration. These 5 participants had acoziborole

exposures within the same ranges as those observed for the other participants and were cured at the end of study. The Applicant proposed to include in the SmPC the instruction to re-administer the dose if vomiting occurs within 15 minutes of administration. Acoziborole is given as a one-time oral administration, and it is most likely that all or most of the dose is lost if vomiting occurs before gastric emptying (15 to 45 minutes in a fasted state). It is not, however, possible to determine what proportion of the dose might be retained despite vomiting after this time period and re-administration leading to supratherapeutic exposures would carry unacceptable safety risks. Therefore, the proposal is acceptable.

In case of relapse and after discussion with the Principal Investigator, the participant had to receive first-line rescue treatment with NECT or pentamidine, depending on the stage of the disease. The use of such rescue medication would be classified as a treatment failure.

The primary endpoint was the success rate at 18 months (M18) in participants with late-stage g-HAT. The estimand framework was not applied in this study. Treatment success and failure were defined according to the WHO criteria, with the adaptation that death was always considered as treatment failure, regardless of cause, uncertainty or missing information. This is considered conservative for analysis of efficacy and thus acceptable. Use of treatment success at 18 months for the primary endpoint was endorsed during earlier CHMP Scientific Advice (EMEA/H/SA/3173/1/2015/III).

The secondary efficacy endpoints encompassed treatment success in late-stage g-HAT at earlier timepoints of M6 and M12, time to proven treatment failure in late-stage g-HAT, as well as at all timepoints in the specific subset of early- and intermediate-stage HAT. These were appropriate.

Statistical methods

Two cohorts of patients were studied: patients with early- or intermediate-stage HAT and patients with late-stage HAT. Those cohorts were analysed separately for most analyses. The primary analysis was an estimate of the success rate at Month 18 and the 95% Jeffreys CI of the estimate. No formal hypothesis test was performed, and no predefined study success criteria was defined.

The primary analysis set for efficacy analysis was the modified intention to treat set (mITT). The mITT set were to exclude patients who fled the region due to armed conflict or natural disaster or due to force majeure and for whom no failure was detected. No patients were excluded for these reasons and hence the mITT set where the same as the Treated set, including all patients who received at least one tablet of acoziborole.

Three futility analyses were performed, and the study was not stopped early at any of these.

Handling of missing data was included in the derivation algorithms for outcome of response variables. Different approaches were used in sensitivity analyses ("Fair case method", "Best case method" and "Observed case method"). The low number of missing data made these sensitivity analyses almost identical to the primary analysis.

The Applicant was recommended in CHMP Scientific Advice (EMEA/H/SA/3173/1/2015/III) to contextualise the observed success rate and lower bound of the 95% confidence interval in light of the external data available for NECT. Success rates with NECT as demonstrated in recent large Phase 3 and 4 (field) studies are high at 95-97%. It was conceded during Scientific Advice that a single-oral dose regimen achieving similar outcomes would represent a clinical advantage, particularly in terms of administration in more remote/isolated locations. The comparisons with external data were performed descriptively using forest plots, which is agreed to be informative for contextualisation of the results. Furthermore, complementary analyses with statistical comparisons across trials were also performed. Those are considered of limited value due to inherent limitations

with between-trial comparisons.

Results

Of the 260 screened subjects serologically positive for g-HAT, 208 were confirmed parasitologically and received the 960 mg single oral dose of acoziborole: 41 participants with early- or intermediate-stage g-HAT and 167 participants with late-stage g-HAT.

Participants were generally young (mean 34.0, range 15.0-68.0 years), with low BMI (mean 20.0, range 15.2-29.7 kg/m2) and 56.3% male.

Two-thirds of the 52 screeing failures failed to meet the inclusion criterion requiring parasitological confirmation and thus were not eligible for treatment in the study. In 40% of cases was exclusion due to not receiving adequate pre-treatment for soil-transmitted helminth and/or malaria infection or, related, in 17.8% exclusion due to not being adequately tested for malaria. This exclusion criterion was primarily for safety reasons, to ensure that co-infections were appropriately managed, although it is acknowledged also that untreated co-infection could have complicated clinical symptom and thus efficacy assessment on trial. A final reason for screening failure was protocol-defined major laboratory abnormality in over half of cases (safety-related exclusion criteria). These screening failures are not considered to impact the assessment of efficacy data.

In general, clinical signs and symptoms of HAT at baseline were more frequently reported in the late-stage HAT cohort compared to the early- and intermediate-stage HAT cohort. A majority (133 of 208 total, 167 late-stage) study participants fell into the baseline severity category E (positive CSF parasitology and CAF WBC ≥20 cells/µl) and thus the study population is considered sufficiently relevant to the sought indication.

There was a large variability in CSF WBC in the late-stage HAT cohort, with values ranging from 6.0 to 2705 cells/µL. Median CSF WBC was 260.0 cells/µL and most patients in the late-stage HAT cohort had CSF WBC >100 cells/µL (76.6% of patients), corresponding to a relatively severe disease population.

All treated participants were included in the mITT, Treated, and PP analysis sets. A high rate of procedures outside allocated time frame (56.6% participants affected) and missed procedures (40.5% participants affected). Protocol deviations related to efficacy measures were infrequent (4% of participants) and involved deviations from protocol-specified timing of only a few days, which does not affect the efficacy assessment. Protocol deviations related to eligibility data collection were infrequent (6%) and ultimately did not lead to inclusion of participants who should have been deemed in eligible. Protocol deviations related to PK data collection (42%) were related to mis-timing of sampling, which is suboptimal but largely mitigated by the fact that actual sampling time was recorded and used for analyses. Protocol deviations relating to assessment of ECG (56%) were largely mis-timing <1 hour outside of protocol-specified window. Given the PK profile of acoziborole, it is agreed that these small temporal deviations are unlikely to affect clinical interpretation. Protocol deviations relating to other safety laboratory parameter assessments (23%) seem to have occurred randomly in terms of affected parameter and participant, such that the overall assessment of safety is not affected.

According to the primary analysis, the success rate at M18 in participants with late-stage g-HAT following acoziborole treatment was high at 95.2% (159/167, 95% CI: [91.2-97.7]%). At M18, 8/167 (4.8%) participants with late-stage g-HAT were considered as treatment failures:
4 participants died of causes assessed by the Investigator and the Sponsor as unrelated to the study drug or HAT disease, 3 participants had relapse, and 1 participant was lost to follow-up. All sensitivity analyses of the primary analysis provided similar results and confirmed the robustness of

the finding.

Untreated late-stage g-HAT is considered an invariably chronic disease with near-zero spontaneous clearance of parasites. Infrequent cases of spontaneous clearance of g-HAT parasites without treatment have been reported in the literature[11]. Precise estimates of the frequency of such spontaneous resolution events are made difficult by the inevitable selection bias introduced when following a cohort of patients who have decided to refuse treatment – these patients exhibited largely asymptomatic/subclinical early disease without progression to classical manifestations. At any rate, these spontaneous events seem to occur after many years of chronic subclinical infection, possibly driven by an as-yet-uncharacterised aspects of host-parasite immune interactions in particular individuals, are not considered the normal clinical course for *T.b. gambiense* infection. Thus, it is considered possible to infer absolute efficacy of the study treatment at M18 in late-stage HAT (i.e. over putative placebo) even in the absence of a placebo arm and considering the "worst case" effect estimate of 91.2% at the lower margin of the 95% CI.

The success rate in late-stage HAT patients was 95.8% (95% CI: 91.9; 98.1) at Month 12 and 94.6% (95% CI: 90.4; 97.3) at Month 6.

The success rate at 6, 12 and 18 months in early- or intermediate-stage HAT patients was 100% (95% CI: 94.1; 100.0). As expected, earlier stages of disease with no or less advanced CNS infection demonstrated earlier, complete and sustained response.

The Jeffreys 95% Credible Interval uses Bayesian methods with the non-informative Jeffreys prior to derive an interval representing the probable range of the parameter. Although it is useful, especially when dealing with small sample sizes or extreme proportions (i.e., near 0% or 100%), it has a Bayesian basis. As requested, the Applicant provided confidence intervals (CIs) for the primary and secondary endpoints using the Clopper-Pearson exact method and compared them with Jeffreys 95% credible intervals from the Bayesian approach. The choice between the Jeffreys 95% credible interval and the Clopper-Pearson 95% CI depends on whether statistical rigor (guaranteed coverage) or efficiency (shorter width) is prioritized. Although the Clopper-Pearson 95% CI is a conservative method, it guarantees at least 95% coverage, but the CIs tend to be overly wide, particularly for small sample sizes. Both methods yielded consistent estimates of the CIs for the success rates with acoziborole and did not affect the interpretation of efficacy. However, as expected, Clopper-Pearson intervals were slightly wider, especially with small sample sizes, such as in early- and intermediate-stage cohorts.

Overall, 8 participants (4.8%) were considered as treatment failures at M18 and all had a late-stage g-HAT. Among these, 4 (2.4%) participants died for causes assessed by the Investigator and the Sponsor as unrelated to the study drug or HAT (Guillain Barré syndrome, poisoning, extrapulmonary tuberculosis, acute pulmonary edema), 3 (1.8%) participants were positive for trypanosomes at M18 and considered with relapse, and 1 (0.6%) participant was lost to follow up at M6. Upon request, the Applicant provided more information about the 3 participants who relapsed. It seems, from data provided, that no co-morbidities or co-medications were reported. However, all three patients had severe late-stage g-HAT at inclusion, with parasites detected in the CSF and WBC count >100 cells/µL, ranging from 455 to 971 cells/µL, which is above the mean observed value for the participants with late-stage g HAT (398.8 ±438.4 cells/µL). Increase in CSF WBC was detected at Month 12 in all patients together with potentially g-HAT-related signs and symptoms. On one side, all the above might reasonably suggest the fact that patients with very severe late-stage g-HAT at baseline could be more susceptible to relapse after treatment, on the other side many participants with more severe baseline disease were successfully treated without relapse. However,

[11] Jamonneau, Vincent, et al. "Untreated human infections by Trypanosoma brucei gambiense are not 100% fatal." PLoS neglected tropical diseases 6.6 (2012): e1691.

the Applicant proposed to include in section 4.4 of the SmPC a warning on risk of relapse after therapy, advising to instruct patients to contact the healthcare provider in case of occurrence of signs/symptoms of relapse. This is agreed.

No information is provided regarding an extended follow up after study termination. The Applicant clarified that no extended follow-up was planned after study termination at 18 months in the protocol of the pivotal study (DNDi-OXA-02-HAT), but it was specified that in case of "uncertain outcome" the Investigator or the study team could plan an additional follow-up visit to collect data or provide rescue treatment at any time point, including at the 18-month time point. None was considered a "probable relapse" or uncertain evolution at the end of the study, i.e., after 18 months of follow-up, indicating the unlikeliness of late relapses.

According to a WHO expert consultation of 2004 concluding that a follow-up of 18 months was sufficient for comparative evaluation of efficacy in clinical trials for new drugs for g-HAT, the Applicant considered to apply to the patients with g-HAT treated with acoziborole, the same WHO advice as for NECT, i.e., "to come for check-up if [g-HAT] symptoms reappear".

All the above said and considering that the only three cases of relapse occurred already at 12 months, it can be agreed with the Applicant's proposal "to come for check-up if [g-HAT] symptoms reappear".

A specific recommendation regarding relapses is proposed in the SmPC and PIL which is supported.

Overall, no significant differences in efficacy results are observed among **age groups**, and a similar response rate, or even slightly better, is found for adolescents and adults.

On-study treatment of concomitant malaria infection

The most frequently reported significant medical history at baseline was malaria (26%) and these participants received artemether/lumefantrine therapy prior to study treatment. Concomitant malaria episodes are likely the most frequent intercurrent infectious events in patients with g-HAT in clinical practice. The artemether-lumefantrine combination given for 3 days is the first-line treatment for non-complicated malaria in most countries where g-HAT is endemic and is highly effective. Artemether activity supports fast clearance of parasites and symptom relief, while lumefantrine provides a post-treatment prophylactic effect by preventing recrudescence (relapse due to surviving parasites) and reinfection. Malaria symptoms usually resolve within 3 days of treatment start. However, both artemether and lumefantrine exposure could potentially be significantly decreased by CYP3A4 induction after acoziborole administration. In study DNDi-OXA-02-HAT, a minimum 3-day washout period was completed after antimalarial treatment before acoziborole administration. This was to avoid interference with ECG assessment (artemisinin-based compounds prolong the QT interval) rather than related to DDI concerns, as the study results of DNDi-OXA-07-HAT were not yet available. In study DNDi-OXA-04-HAT, no washout period was required before acoziborole administration.

A very small number of participants (7) were treated concomitantly during the period of strongest induction of CYP3A4 by acoziborole and were documented as *"Recovered"*. A further 17 participants received antimalarial treatment between days 31 and 84 and all are documented as recovered. However, outcome of antimalarial treatment was not determined parasitologically nor were recurrences distinguished from reinfections amongst participants experiencing two on-study episodes of malaria infection (12). No PK data were collected artemether and lumefantrine. An absence of unsolicited TEAEs that might be attributable to DDI is not a sufficiently sensitive alternative approach to exclude a potentially clinically relevant DDI. The authorised SmPC for Riamet include in 4.3 a contraindication in "patients taking drugs that are strong inducers of CYP3A4 such as rifampin". The very limited clinical data presented in the dossier are not considered sufficient to

negate the similarly strong and thus clinically relevant interaction anticipated between acoziborole and artemether-lumefantrine such that co-administration can be recommended. The SmPC has been amended to contraindicate co-administration of artemether/lumefantrine during the first month after acoziborole administration and recommend caution due to potentially decreased effect with co-administration between 1 and 3 months after acoziborole administration.

Special populations

The pivotal efficacy study DNDi-OXA-02-HAT excluded clinically significant medical conditions other than g-HAT, such as significant liver or renal disease. Pregnant women and paediatric patients <15 years of age were excluded from the study, and older patients ≥65 years of age are not well represented. Dose adjustment in older patients and renal impairment is not necessary based on popPK analyses (see Pharmacokinetics). Acoziborole is primarily eliminated by hepato-biliary clearance and its hepatic metabolism is limited and slow, therefore use in patients with hepatic impairment is not recommended.

Analysis performed across trials

The Applicant was recommended in CHMP Scientific Advice (EMEA/H/SA/3173/1/2015/III) to contextualise the observed success rate and lower bound of the 95% confidence interval in light of the external data available for NECT. Success rates with fexinidazole and NECT as demonstrated in recent large Phase 3 and 4 (field) studies are high at 91-97%. It was conceded during Scientific Advice that a single-oral dose regimen achieving similar outcomes would represent a clinical advantage, particularly in terms of administration in more remote/isolated locations. The DNDi-OXA-02-HAT study population was sufficiently similar to previous clinical studies for NECT and fexinidazole so as to permit contextualisation using these data.

Four randomized clinical trials with NECT, including the NECT control arm from the pivotal fexinidazole trial and the fexinidazole arm from its pivotal trial, were considered for the indirect comparison meta-analysis. In addition, a case series study with NECT was included in the analysis.

The efficacy point estimate from study DNDi-OXA-02-HAT was similar to previous studies of NECT and fexinidazole with respect to point estimate. None of these trials include a placebo arm, which would not be ethically supportable. This is not considered problematic for the purposes of contextualisation. The point estimate has better precision/ a narrower confidence interval versus some of the smaller historical studies, with a lower bound of the 95% CI in line with or above those reported for NECT and fexinidazole studies, as can be seen most easily from the forest plot presentation (see Figure 21). It is considered that this descriptive contextualisation supports the similar efficacy of acoziborole for the treatment of trypanosomiasis and its utility amongst existing therapeutic options.

To further support comparability with the external control groups (both NECT and fexinidazole), the Applicant clarified that a systematic literature search in PubMed and Clinicaltrials.gov was performed to retrieve all published clinical studies (randomized controlled/single-arm trials, observational studies, and case series) in g-HAT patients that contained at least one treatment group treated with NECT or fexinidazole. Among 33 referenced studies, 6 were selected based on similar characteristics, i.e., study population, confirmed second- or late-stage g-HAT, and consistent timing of outcome assessment, defined as cure or probable cure based on WHO criteria.

Although the selected studies enrolled participants with confirmed g-HAT (predominantly late-stage disease) with similar age and sex distributions to DNDi-OXA-02-HAT, they were conducted in areas with a different epidemiological status of the disease. In addition, the criteria for disease stage diagnosis were not the same in all studies.

Therefore, a complementary efficacy analysis was performed considering only the 3 largest NECT studies for which raw individual data were available, stratifying patients into 3 categories (non-severe/severe/very severe) and using the propensity score (based on disease severity, age, and sex) for the adjusted indirect statistical comparisons between acoziborole, NECT, and fexinizadole.

Labelling

The wording of the claimed indication *[(is indicated for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic) human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense (g-HAT)]* seems not completely aligned to the WHO 2024 classification, which also encompasses the severe second-stage *(⩾ 100 WBC/ μL with OR without trypanosomes in CSF),* a patient subpopulation included in the pivotal study. In order to avoid prescriber's misunderstandings and considering that acoziborole has shown to be effective across disease severity stages, the applicant agreed to add "*severe second-stage (⩾ 100 White Blood Cell/μL with or without trypanosomes in cerebrospinal fluid)"* to the therapeutic indication.

5.3.4.2. Conclusions on the clinical efficacy

The efficacy of the 960 mg single-dose regimen of acoziborole in patients ≥15 years of age, regardless of g-HAT stage at baseline, has been established from the single pivotal study DNDi-OXA-02-HAT.

5.4. Clinical safety

The safety database constitutes of two phase II/III studies (DNDi-OXA-02-HAT, DNDi-OXA-04-HAT) executed in Guinea and DRC, of which DNDi-OXA-02-HAT is considered the pivotal study. In addition, safety data from three phase I studies executed in France, UK and Malaysia has been presented (DNDiOXA001, DNDi-OXA-03-HAT, DNDi-OXA-07-HAT).

DNDi-OXA-02-HAT is a single-arm, multicenter, open label study evaluating efficacy and safety. The study included only participants with parasitologically confirmed early, intermediate or late-stage g-HAT. A single oral dose of acoziborole 960 mg were administered to 208 participants ≥15 years at fasting state, the study duration was 18 months. This study is considered as the pivotal study for this application.

DNDi-OXA-04-HAT is a placebo-controlled, double-blind study including participants seropositive to g-HAT (not parasitologically confirmed) to evaluate safety and tolerability. A single oral dose of either acoziborole 960 mg (n=906) or placebo (n=300) were administered to participants ≥15 years at fasting state, the study duration was 4 months.

DNDiOXA001 is a phase I study evaluating ascending doses of acoziborole as a single oral dose (20-1200 mg) and included 128 healthy male adults. The participants were followed up to 6 months.

DNDi-OXA-03-HAT is a phase I study evaluating mass balance recovery, metabolite profile and metabolite identification in a total of 6 participants.

DNDi-OXA-07-HAT is a phase I study evaluating drug interaction of 960 mg acoziborole with sequential co-administration of oral midazolam and dextromethorphan in 20 healthy male adults.

Definitions

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Study DNDi-OXA-02-HAT included participants with parasitologically confirmed g-HAT at different stages. The participants underwent screening and Day -15 to Day -1 and baseline assessment between Day -4 to -1. The participants were at the hospital from Day 1 to 15 for observation which included clinical evaluations, neurological examinations, haematological and biochemistry analysis. Follow-up visits were performed on Month 3, 6, 12 and 18 after dose administration. In addition, the patient was supposed to return to the investigational centre if s/he did not feel well, even if there was no apparent relationship with treatment or HAT. Digital ECG recordings as well as heart rate examination were executed on Day 1 (4- and 9-hours post dose), Day 2 (24 h), Day 3 (48 h), Day 4 (72 h), Day 5 (96 h) and day 11 (240 h). For vital signs, clinical examination, neurological examination, haematology, biochemistry, thyroid function test was recorded.

Study DNDi-OXA-04-HAT included participants seropositive to g-HAT but not parasitologically confirmed diagnosis. The participants underwent screening and were hospitalized for at least one day before treatment. The participants were randomized 3:1 to acoziborole 960 mg or placebo, and they remained in hospital for 5 days for observation after administration. The study included follow-up at hospital one-month post-dose and contact with investigator two and three months after administration. The study was completed after the four-month visit have occurred at the hospital. Unscheduled visit could occur if needed during the study. ECG were recorded pre-dose D1 and D5 post dose. For vital signs, clinical examination, blood pressure, hematology and biochemistry were recorded.

No restrictions or specific recommendations were provided in the study protocols regarding DDI and coadministration with CYPs substrates in the clinical studies.

The phase I studies are further described in section 2 "clinical pharmacology".

5.4.2. Patient exposure

Table 22. Patient exposure (Single arm study cut off 08 Sept 2020; Placebo controlled study cut off 03 Aug 2023)

	Patients enrolled	***Patients exposed****	***Patients exposed to the proposed dose range***	***Patients with long term** safety data***
Blinded studies (placebo-controlled)	1208	1206 (n=906 acoziborole; n=300 placebo	906	0
Blinded studies (active - controlled)	-	-	-	-
Single arm study	260	208	208	203
Post marketing	-	-	-	-
Compassionate use	-	-	-	-

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Study DNDi-OXA-02-HAT started on 11 OCT 2016, ended 08 SEPT 2020, and were executed in DRC (n=174) and Guinea (n=34). Among the 208 participants aged 15-68 years that received acoziborole, 41 participants had early, or intermediate stage of g-HAT and 167 participants were diagnosed with late-stage g-HAT. In total a slightly higher number of participants were male (n=117 [56%]). Initially 260 participants were enrolled, the 52 subjects that did not receive the treatment mainly due to not meeting the inclusion criteria or meeting the exclusion criteria (n=43), are further discussed in the efficacy section.

Malaria was the most reported medical history (26%) followed by ECG T-wave inversion (15%) and anaemia (8%). In this study, all participants received benzimidazole before study start as treatment for soil-transmitted helminthiasis. All participants with positive malaria test received treatment before study start (n=55) i.e. artemether/lumefantrine therapy. At baseline the mean body weight of all 208 participants was 57,6 kg (±10,5 kg) with a range 33 kg-100 kg.

All 208 (100%) participants with g-HAT included in study DNDi-OXA-02-HAT received the full single oral dose of acoziborole at 960 mg (3 × 320 mg) on Day 1.

Study DNDi-OXA-04-HAT started on 30 DEC 2021, ended 03 Aug 2023. A total of 1266 participants were screened, and 1208 patients were eligible for inclusion, the main reason for screening failure were medical conditions and/or abnormal laboratory test results. The study was executed in DRC (n=1030) and Guinea (n=176) and included participants aged 15-90 years. A slightly higher number of treated subjects were female (n=476 [52,5%]). Of the 1208 participants, 1196 completed the study. Nine participants in the acoziborole group (n=7 lost to follow up; n=2 withdrawal of consent) and three participants in the placebo group (n=1 death; n=1 lost to follow up; n=1 withdrawal of consent) discontinued the study. The medical history was within similar frequency for both placebo and the treatment group, where menopause (13%), gastritis (6%) and appendicectomy (4%) were most reported. The most frequent prior medication was paracetamol (0,8%) and aluminium hydroxide (0,7%).

At baseline the mean body weight of all the 906 participants receiving acoziborole was 52 kg (range 30

kg-109,5 kg), and for the 300 participants in the placebo group the mean body weight was 51,7 kg (range 30 kg-85 kg). In the acoziborole arm the mean age was 37,4 years (range 15-90 years) and in the placebo arm the mean age was 36,4 years (range 15-74 years). Overall, 47% of the participants was male and 53% female. The mean Body Mass Index (BMI) overall was 20,1 (range 15,1-41,2).

All 1208 (100%) of the participants seropositive for g-HAT received either a single oral dose of acoziborole at 960 mg (3 x 320 mg) or placebo on Day 1.

5.4.3. Adverse events

5.4.3.1. Participants with g-HAT (Study DNDi-OXA-02-HAT)

The summary of AEs and TEAEs that occurred in participants diagnosed with g-HAT in study DNDi-OXA-02-HAT up to Month 18 is presented in Table 23, below.

Table 23. Overview of adverse events in participants with g-HAT (Treated set) – study DNDi-OXA-02-HAT

Safety parameter Number of participants (%) [95% Jeffreys CI]	Early and Intermediate stage (N = 41)	Late stage (N = 167)	Total (N = 208)
At least one AE[a]	**33 (80.5%)** **[66.5%; 90.3%]**	**136 (81.4%)** **[75.0%; 86.8%]**	**169 (81.3%)** **[75.5%; 86.1%]**
At least one TEAE[a]	**28 (68.3%)** **[53.2%; 80.9%]**	**127 (76.0%)** **[69.2%; 82.0%]**	**155 (74.5%)** **[68.3%; 80.1%]**
Mild to moderate TEAE[b]	27 (65.9%) [50.7%; 78.9%]	127 (76.0%) [69.2%; 82.0%]	154 (74.0%) [67.8%; 79.6%]
Severe TEAE[b]	4 (9.8%) [3.4%; 21.5%]	24 (14.4%) [9.7%; 20.3%]	28 (13.5%) [9.3%; 18.6%]
Drug-related TEAE	2 (4.9%) [1.0%; 14.7%]	27 (16.2%) [11.2%; 22.3%]	29 (13.9%) [9.7%; 19.1%]
Severe drug-related TEAE	0 (0.0%) [0.0%; 5.9%]	0 (0.0%) [0.0%; 1.5%]	0 (0.0%) [0.0%; 1.2%]
At least one serious TEAE	**3 (7.3%)** **[2.1%; 18.3%]**	**18 (10.8%)** **[6.8%; 16.1%]**	**21 (10.1%)** **[6.6%; 14.7%]**
Serious drug-related TEAE	0 (0.0%) [0.0%; 5.9%]	0 (0.0%) [0.0%; 1.5%]	0 (0.0%) [0.0%; 1.2%]
Serious TEAE leading to death	0 (0.0%)	4 (2.4%)	4 (1.9%)

Abbreviations: **AE**, adverse event; **CI**, confidence interval; **CTCAE**, Common Toxicity Criteria for Adverse Events; **g-HAT**, human African trypanosomiasis due to *T. b. gambiense*; **TEAEs**, treatment-emergent adverse event.

a Definition in Table 2.

b A mild event corresponded to CTCAE Grade 1, a moderate event to CTCAE Grade 2 and a severe event to CTCAE Grades 3-5.

In study -02, at least one TEAEs (ie AEs occurring on or after the date of administration of acoziborole up to study end) were reported in 68% of the participant with early and intermediate stage g-HAT of which 10% were severe and 5% were considered related to acoziborole. In the participants with late-stage g-HAT, 76% reported at least one TEAE of which 14% were severe and 16% were considered related to acoziborole.

From Day 1 up to 18 months after treatment, the most reported SOCs were injury, poisoning and procedural complications (31%), of which a slightly higher frequency was observed in the early/intermediate stage (42%) compared with late stage (34%). Nervous system disorders were

reported in 31% in total (early/intermediate 34%; late 31%) and infections and infestations at a frequency of 31% (early/intermediate 20%; late 34%). As illustrated in Table 24, the most reported PT in all stages of g-HAT were associated with the lumbar puncture: procedural pain (25%) and procedural headache (15%). Other commonly reported PTs for the entire study population were headache (25%) pyrexia (15%) and malaria (14%).

Table 24. Overview of all TEAEs reported in >1% of participants by system organ class and preferred term (Treated set) - Study DNDi-OXA-02-HAT

SOC/PT Number of participants (%) *number of events*	Early and Intermediate stage (N = 41)	Late stage (N = 167)	Total (N = 208)
At least one TEAE	**28 (68.3%) *99***	**127 (76.0%) *501***	**155 (74.5%) *600***
Injury, poisoning and procedural complications	**17 (41.5%) *31***	**56 (33.5%) *72***	**73 (35.1%) *103***
Procedural pain	13 (31.7%) *17*	39 (23.4%) *46*	52 (25.0%) *63*
Procedural headache	11 (26.8%) *13*	21 (12.6%) *22*	32 (15.4%) *35*
Nervous system disorders	**14 (34.1%) *16***	**51 (30.5%) *68***	**65 (31.3%) *84***
Headache	12 (29.3%) *14*	39 (23.4%) *49*	51 (24.5%) *63*
Tremor	0 (0.0%) *0*	6 (3.6%) *7*	6 (2.9%) *7*
Dizziness	0 (0.0%) *0*	3 (1.8%) *3*	3 (1.4%) *3*
Infections and infestations	**8 (19.5%) *12***	**57 (34.1%) *103***	**65 (31.3%) *115***
Malaria	5 (12.2%) *5*	24 (14.4%) *29*	29 (13.9%) *34*
Urinary tract infection	1 (2.4%) *1*	7 (4.2%) *10*	8 (3.8%) *11*
Diarrhea infectious	2 (4.9%) *2*	5 (3.0%) *6*	7 (3.4%) *8*
Gastroenteritis	0 (0.0%) *0*	5 (3.0%) *7*	5 (2.4%) *7*
Thyphoid fever	0 (0.0%) *0*	5 (3.0%) *5*	5 (2.4%) *5*
Viral upper respiratory tract infection	0 (0.0%) *0*	5 (3.0%) *5*	5 (2.4%) *5*
Influenza	1 (2.4%) *1*	3 (1.8%) *3*	4 (1.9%) *4*
Wound infection	1 (2.4%) *1*	3 (1.8%) *3*	4 (1.9%) *4*
Abscess	0 (0.0%) *0*	3 (1.8%) *3*	3 (1.4%) *3*
Conjunctivitis	0 (0.0%) *0*	3 (1.8%) *3*	3 (1.4%) *3*
Infection parasitic	0 (0.0%) *0*	3 (1.8%) *3*	3 (1.4%) *3*
Respiratory tract infection	0 (0.0%) *0*	3 (1.8%) *3*	3 (1.4%) *3*
General disorders and administration site conditions	**9 (22.0%) *9***	**40 (24.0%) *55***	**49 (23.6%) *64***
Pyrexia	4 (9.8%) *4*	27 (16.2%) *30*	31 (14.9%) *34*
Asthenia	5 (12.2%) *5*	13 (7.8%) *14*	18 (8.7%) *19*
Edema peripheral	0 (0.0%) *0*	3 (1.8%) *3*	3 (1.4%) *3*
Gastrointestinal disorders	**2 (4.9%) *2***	**32 (19.2%) *40***	**34 (16.3%) *42***
Vomiting	0 (0.0%) *0*	13 (7.8%) *14*	13 (6.3%) *14*
Abdominal pain	0 (0.0%) *0*	8 (4.8%) *9*	8 (3.8%) *9*
Nausea	0 (0.0%) *0*	5 (3.0%) *5*	5 (2.4%) *5*
Abdominal pain upper	0 (0.0%) *0*	3 (1.8%) *3*	3 (1.4%) *3*
Investigations	**5 (12.2%) *5***	**27 (16.2%) *31***	**32 (15.4%) *36***
Weight increased	1 (2.4%) *1*	19 (11.4%) *19*	20 (9.6%) *20*
Weight decreased	0 (0.0%) *0*	6 (3.6%) *6*	6 (2.9%) *6*

SOC/PT Number of participants (%) *number of events*	Early and Intermediate stage (N = 41)	Late stage (N = 167)	Total (N = 208)
Psychiatric disorders	**2 (4.9%) *2***	**28 (16.8%) *40***	**30 (14.4%) *42***
Insomnia	2 (4.9%) *2*	13 (7.8%) *16*	15 (7.2%) *18*
Abnormal behaviour	0 (0.0%) *0*	6 (3.6%) *6*	6 (2.9%) *6*
Musculoskeletal and connective tissue disorders	**6 (14.6%) *6***	**20 (12.0%) *23***	**26 (12.5%) *29***
Back pain	3 (7.3%) *3*	10 (6.0%) *11*	13 (6.3%) *14*
Neck pain	1 (2.4%) *1*	4 (2.4%) *4*	5 (2.4%) *5*
Arhralgia	0 (0.0%) *0*	4 (2.4%) *4*	4 (1.9%) *4*
Skin and subcutaneous tissue disorders	**3 (7.3%) *4***	**14 (8.4%) *17***	**17 (8.2%) *21***
Pruritus	1 (2.4%) *1*	7 (4.2%) *7*	8 (3.8%) *8*
Urticaria	1 (2.4%) *1*	2 (1.2%) *3*	3 (1.4%) *4*
Metabolism and nutrition disorders	**4 (9.8%) *4***	**12 (7.2%) *12***	**16 (7.7%) *16***
Decrease appetite	2 (4.9%) *2*	4 (2.4%) *4*	6 (2.9%) *6*
Obesity	1 (2.4%) *1*	2 (1.2%) *2*	3 (1.4%) *3*
Overweight	1 (2.4%) *1*	2 (1.2%) *2*	3 (1.4%) *3*
Respiratory, thoracic and mediastinal disorders	**1 (2.4%) *1***	**9 (5.4%) *9***	**10 (4.8%) *10***
Cough	1 (2.4%) *1*	2 (1.2%) *2*	3 (1.4%) *3*
Blood and lymphatic system disorders	**1 (2.4%) *1***	**7 (4.2%) *7***	**8 (3.8%) *8***
Anemia	1 (2.4%) *1*	6 (3.6%) *6*	7 (3.4%) *7*
Cardiac disorders	**1 (2.4%) *1***	**7 (4.2%) *8***	**8 (3.8%) *9***
Atrioventricular block first degree	0 (0.0%) *0*	4 (2.4%) *4*	4 (1.9%) *4*
Reproductive system and breast disorders	**2 (4.9%) *2***	**4 (2.4%) *6***	**6 (2.9%) *8***
Amenorrhea	2 (4.9%) *2*	2 (1.2%) *2*	4 (1.9%) *4*

Abbreviations: **PT**, preferred term; **SOC**, system organ class; **TEAE**, treatment-emergent adverse event.

In total, 44 severe TEAEs were reported by 28 participants, of which anaemia (1,9%), malaria (1,9%), headache (1,4%) were most reported. None of the severe TEAEs were considered related to treatment by the investigator. During the hospitalization (D1-14) did 16 participant report severe TEAEs and after hospitalisation 17 participants reported severe TEAEs.

As illustrated in Table 25, which presents reported SOCs and PTs during hospitalization, more participants (n=127) reported TEAEs during the initial two weeks after administration of the treatment during hospitalization than at the time from hospitalization up to EoS (18 months) where 99 participants reported TEAEs.

Table 25. By cohort and overall

	Cohort								
	Stage 1 and Intermediate (N=41)			Stage2 (N=167)			Total (N=208)		
Primary System Organ Class / Dictionary-Derived Term	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat
ANY ADVERSE EVENTS	58	26	63.4	250	101	60.5	308	127	61.1
Blood and lymphatic system disorders	1	1	2.4	4	4	2.4	5	5	2.4
- Anaemia	1	1	2.4	4	4	2.4	5	5	2.4
Cardiac disorders	.	.	.	7	6	3.6	7	6	2.9
- Atrioventricular block first degree	.	.	.	4	4	2.4	4	4	1.9
- Chest pain	.	.	.	1	1	0.6	1	1	0.5
- Tachycardia	.	.	.	2	1	0.6	2	1	0.5
Ear and labyrinth disorders	.	.	.	1	1	0.6	1	1	0.5
- Tinnitus	.	.	.	1	1	0.6	1	1	0.5
Eye disorders	.	.	.	2	2	1.2	2	2	1.0
- Eye pruritus	.	.	.	1	1	0.6	1	1	0.5
- Ocular hyperaemia	.	.	.	1	1	0.6	1	1	0.5
Gastrointestinal disorders	1	1	2.4	23	20	12.0	24	21	10.1
- Abdominal pain	.	.	.	7	7	4.2	7	7	3.4
- Abdominal pain upper	.	.	.	3	3	1.8	3	3	1.4
- Anal haemorrhage	.	.	.	1	1	0.6	1	1	0.5
- Constipation	.	.	.	1	1	0.6	1	1	0.5
- Gastritis	.	.	.	1	1	0.6	1	1	0.5
- Nausea	.	.	.	1	1	0.6	1	1	0.5
- Toothache	1	1	2.4	.	.	.	1	1	0.5
- Vomiting	.	.	.	9	8	4.8	9	8	3.8
General disorders and administration site conditions	5	5	12.2	21	18	10.8	26	23	11.1
- Asthenia	4	4	9.8	10	9	5.4	14	13	6.3
- Chest pain	.	.	.	1	1	0.6	1	1	0.5
- Chills	.	.	.	1	1	0.6	1	1	0.5
- Feeling hot	.	.	.	1	1	0.6	1	1	0.5
- Influenza like illness	.	.	.	1	1	0.6	1	1	0.5
- Oedema peripheral	.	.	.	1	1	0.6	1	1	0.5
- Pyrexia	1	1	2.4	6	6	3.6	7	7	3.4
Infections and infestations	4	4	9.8	29	24	14.4	33	28	13.5
- Abscess	.	.	.	2	2	1.2	2	2	1.0
- Conjunctivitis	.	.	.	1	1	0.6	1	1	0.5
- Diarrhoea infectious	2	2	4.9	5	4	2.4	7	6	2.9
- Enteritis infectious	.	.	.	2	2	1.2	2	2	1.0
- Gastroenteritis	.	.	.	4	4	2.4	4	4	1.9

- Infection parasitic	.	.	.	1	1	0.6	1	1	0.5
- Influenza	.	.	.	2	2	1.2	2	2	1.0
- Malaria	2	2	4.9	4	4	2.4	6	6	2.9
- Typhoid fever	.	.	.	1	1	0.6	1	1	0.5
- Urinary tract infection	.	.	.	2	2	1.2	2	2	1.0
- Varicella	.	.	.	1	1	0.6	1	1	0.5
- Viral upper respiratory tract infection	.	.	.	4	4	2.4	4	4	1.9
Injury, poisoning and procedural complications	26	16	39.0	50	43	25.7	76	59	28.4
- Procedural dizziness	.	.	.	1	1	0.6	1	1	0.5
- Procedural headache	11	10	24.4	19	19	11.4	30	29	13.9
- Procedural pain	15	12	29.3	29	28	16.8	44	40	19.2
- Scratch	.	.	.	1	1	0.6	1	1	0.5
Investigations	2	2	4.9	10	8	4.8	12	10	4.8
- Blood calcium decreased	2	2	4.9	.	.	.	2	2	1.0
- Blood creatinine increased	.	.	.	1	1	0.6	1	1	0.5
- Blood glucose increased	.	.	.	1	1	0.6	1	1	0.5
- Blood potassium increased	.	.	.	1	1	0.6	1	1	0.5
- Blood sodium decreased	.	.	.	2	2	1.2	2	2	1.0
- Weight decreased	.	.	.	1	1	0.6	1	1	0.5
- Weight increased	.	.	.	4	4	2.4	4	4	1.9
Metabolism and nutrition disorders	1	1	2.4	3	3	1.8	4	4	1.9
- Decreased appetite	1	1	2.4	1	1	0.6	2	2	1.0
- Dehydration	.	.	.	1	1	0.6	1	1	0.5
- Malnutrition	.	.	.	1	1	0.6	1	1	0.5
Musculoskeletal and connective tissue disorders	5	5	12.2	17	16	9.6	22	21	10.1
- Arthralgia	.	.	.	4	4	2.4	4	4	1.9
- Back pain	2	2	4.9	7	6	3.6	9	8	3.8
- Bone pain	1	1	2.4	1	1	0.6	2	2	1.0
- Musculoskeletal pain	1	1	2.4	.	.	.	1	1	0.5
- Myalgia	.	.	.	1	1	0.6	1	1	0.5
- Neck pain	1	1	2.4	3	3	1.8	4	4	1.9
- Pain in extremity	.	.	.	1	1	0.6	1	1	0.5
Nervous system disorders	10	9	22.0	42	32	19.2	52	41	19.7
- Dizziness	.	.	.	1	1	0.6	1	1	0.5
- Formication	1	1	2.4	.	.	.	1	1	0.5
- Guillain-Barre syndrome	.	.	.	1	1	0.6	1	1	0.5
- Headache	9	8	19.5	30	24	14.4	39	32	15.4

- Intracranial pressure increased	.	.	.	1	1	0.6	1	1	0.5
- Motor dysfunction	.	.	.	1	1	0.6	1	1	0.5
- Paraesthesia	.	.	.	2	2	1.2	2	2	1.0
- Seizure	.	.	.	1	1	0.6	1	1	0.5
- Tremor	.	.	.	5	4	2.4	5	4	1.9
Psychiatric disorders	.	.	.	21	15	9.0	21	15	7.2
- Abnormal behaviour	.	.	.	5	5	3.0	5	5	2.4
- Anxiety	.	.	.	1	1	0.6	1	1	0.5
- Bipolar I disorder	.	.	.	1	1	0.6	1	1	0.5
- Enuresis	.	.	.	5	2	1.2	5	2	1.0
- Insomnia	.	.	.	7	5	3.0	7	5	2.4
- Psychotic disorder	.	.	.	2	2	1.2	2	2	1.0
Renal and urinary disorders	.	.	.	1	1	0.6	1	1	0.5
- Chromaturia	.	.	.	1	1	0.6	1	1	0.5
Reproductive system and breast disorders	.	.	.	1	1	0.6	1	1	0.5
- Menorrhagia	.	.	.	1	1	0.6	1	1	0.5
Respiratory, thoracic and mediastinal disorders	1	1	2.4	4	4	2.4	5	5	2.4
- Cough	1	1	2.4	1	1	0.6	2	2	1.0
- Rhinitis allergic	.	.	.	2	2	1.2	2	2	1.0
- Rhinorrhoea	.	.	.	1	1	0.6	1	1	0.5
Skin and subcutaneous tissue disorders	2	2	4.9	12	11	6.6	14	13	6.3
- Blister	1	1	2.4	.	.	.	1	1	0.5
- Decubitus ulcer	.	.	.	1	1	0.6	1	1	0.5
- Dermatitis contact	.	.	.	1	1	0.6	1	1	0.5
- Papule	.	.	.	1	1	0.6	1	1	0.5
- Pruritus	.	.	.	6	6	3.6	6	6	2.9
- Rash maculo-papular	1	1	2.4	.	.	.	1	1	0.5
- Skin disorder	.	.	.	1	1	0.6	1	1	0.5
- Urticaria	.	.	.	2	2	1.2	2	2	1.0
Vascular disorders	.	.	.	2	2	1.2	2	2	1.0
- Hypertension	.	.	.	1	1	0.6	1	1	0.5
- Hypotension	.	.	.	1	1	0.6	1	1	0.5

During the study, 44 severe TEAEs were reported by 28 participants, of which anaemia (1,9%), malaria (1,9%), headache (1,4%) were most reported. None of the severe TEAEs were considered related to treatment by the investigator. During the hospitalization (D1-14) did 16 participant report severe TEAEs and after hospitalisation 17 participants reported severe TEAEs.

5.4.3.2. Other study populations (Study DNDi-OXA-04-HAT)

In study DNDi-OXA-04-HAT, no AE was reported in the participants before drug administration on Day 1. Therefore, only the incidence of TEAEs was reported. The summary Table 26 displays the percentage of participants seropositive for g-HAT who experienced at least one TEAE in each arm overall, by age group, sex, severity category, seriousness and period of occurrence, and the ER % of occurrence in the Safety analysis set.

Table 26. Overview of TEAEs in participants seropositive for g-HAT (Safety set) – study DNDi-OXA-04-HAT

TEAE by category	Acoziborole arm n/N (%)	Placebo arm n/N (%)	ER % (95% CI)
At least one TEAE	**195/906 (21.5)**	**69/300 (23.0)**	**-1.5% (-7.2; 3.7)**
At least one TEAE, by age group			
Adolescent (15-17 years)	17/101 (16.8)	4/28 (14.3)	2.5% (-15.7; 14.6)
Adult (≥18 years)	178/805 (22.1)	65/272 (23.9)	-1.8% (-7.8; 3.8)
At least one TEAE, by sex			
Male	78/430 (18.1)	26/142 (18.3)	-0.2% (-8.1; 6.6)
Female	117/476 (24.6)	43/158 (27.2)	-2.6% (-10.9; 4.9)
At least one TEAE, by severity category			
Mild/moderate	183/906 (20.2)	65/300 (21.7)	-1.5% (-7.1; 3.6)
Severe non-related	18/906 (2.0)	8/300 (2.7)	-0.7% (-3.3; 1.1)
Severe related	0	0	NA
At least one TEAE, by seriousness category			
Any serious TEAEs	3/906 (0.3)	4/300 (1.3)	-1.0% (-3.1; 0.0)
Any non-serious TEAEs	193/906 (21.3)	68/300 (22.7)	-1.4% (-7.0; 3.8)
At least one TEAE, by period of occurrence			
During hospitalization	124/906 (13.7)	38/300 (12.7)	1.0% (-3.7; 5.1)
After hospitalization	106/906 (11.7)	45/300 (15.0)	-3.3% (-8.2; 0.9)

Abbreviations: **CI**, confidence interval; **ER**, excess rate; **g-HAT**, human African trypanosomiasis due to *T. b. gambiense*; **TEAEs**, treatment-emergent adverse event.

At least one TEAE was reported in 195 (21,5%) participants in the acoziborole group, and in 69 (23%) participants in the placebo group. A slightly higher frequency of TEAEs were reported in female than men in both the acoziborole group (24,6% vs 18%) and the placebo group (27% vs 18%). The similar frequency between the groups suggest that the difference is not related to treatment. During the five days of hospitalization a similar frequency of TEAEs were reported in the two groups (acoziborole 13,7%; placebo 12,7%), the same pattern was noted the following almost 4 months up to EoS where 11,7% in the acoziborole group and 15% of the participants in the placebo group reported TEAEs

The most frequently reported PTs were headache (acoziborole 5,8%; placebo 2,7%), malaria (3,8% vs 4,7%) and abdominal pain (2,5% vs 3%), see Table 27. Headache and abdominal pain are included as ADRs in the product information at frequency common and uncommon, respectively.

Table 27. Occurrence and ER of TEAS in≥ 1% of participants in either arm by system organ calss and preferred term (Safety set) – Study DNDi-OXA-04-HAT

SOC/PT Number of participants (%) [number of events]	Acoziborole arm N = 906	Placebo arm N = 300	Excess rate ER (95% CI)
Infections and infestations	**74 (8.2) [92]**	**24 (8.0) [32]**	**NA**
Malaria	34 (3.8) [35]	14 (4.7) [14]	-0.9 (-4.1; 1.4)
Acarodermatitis	13 (1.4) [13]	3 (1.0) [3]	0.4 (-1.6; 1.6)
Gastrointestinal disorders	**52 (5.7) [61]**	**21 (7.0) [25]**	**NA**
Abdominal pain	23 (2.5) [23]	9 (3.0) [10]	-0.5 (-3.2; 1.4)
Enteritis	7 (0.8) [7]	4 (1.3) [4]	-0.6 (-2.6; 0.6)
Nausea	7 (0.8) [7]	3 (1.0) [3]	-0.2 (-2.2; 0.8)
Gastritis	6 (0.7) [6]	3 (1.0) [3]	-0.3 (-2.3; 0.7)
Nervous system disorders	**62 (6.8) [68]**	**10 (3.3) [11]**	**NA**
Headache	53 (5.8) [54]	8 (2.7) [9]	3.2 (0.3; 5.3)
General disorders and administration site conditions	**22 (2.4) [22]**	**6 (2.0) [6]**	**NA**
Fatigue	14 (1.5) [14]	5 (1.7) [5]	-0.1 (-2.4; 1.3)
Investigations	**14 (1.5) [15]**	**11 (3.7) [12]**	**NA**
Blood potassium increased	8 (0.9) [8]	6 (2.0) [7]	-1.1 (-3.5; 0.3)

Abbreviations: **CI**, confidence interval; **ER**, excess rate; **NA**, not available; **PT**, preferred term; **SOC**, system organ class; **TEAE**, treatment-emergent adverse event.

The majority of the TEAEs were of mild or moderate severity: at least 1 mild/moderate event was reported in 20.2% of participants in the acoziborole arm and 21.7% of participants in the placebo arm, see Table Table 31 below.

Table 28. Occurrence of treatment adverse events (TIEAE) and excess rate by treatment group – Safety set (SS)

	Acoziborole xx/N (%)	Placebo xx/N (%)	Excess Rate xx% (95% CI)
At least one TEAE	195/906 (21.5%)	69/300 (23.0%)	-1.5% (-7.2 : 3.7)
Age Group			
Adolescent (15-17 years)	17/101 (16.8%)	4/28 (14.3%)	2.5% (-15.7 : 14.6)
Adult (≥ 18 years)	178/805 (22.1%)	65/272 (23.9%)	-1.8% (-7.8 : 3.8)
Sex			
Males	78/430 (18.1%)	26/142 (18.3%)	-0.2% (-8.1 : 6.6)
Females	117/476 (24.6%)	43/158 (27.2%)	-2.6% (-10.9 : 4.9)
TEAE Severity Categorization			
Any serious TEAEs	3/906 (0.3%)	4/300 (1.3%)	-1.0% (-3.1 : 0.0)
Any mild/moderate TEAEs	183/906 (20.2%)	65/300 (21.7%)	-1.5% (-7.1 : 3.6)
Severe not related TEAEs	18/906 (2.0%)	8/300 (2.7%)	-0.7% (-3.3 : 1.1)
Severe drug related TEAEs	0	0	NA
Period of Occurrence Categorization			
During hospitalization	124/906 (13.7%)	38/300 (12.7%)	1.0% (-3.7 : 5.1)
After hospitalization	106/906 (11.7%)	45/300 (15.0%)	-3.3% (-8.2 : 0.9)

Note: CIs calculated using Wilson's score method.
Note: Severe TEAEs have been considered as TEAEs of CTCAE grade 3 or 4.

In total reported 26 participants (2,2%) 29 TEAEs of severe intensity, of which 21 events in 2.0% of participants in the acoziborole arm, and 8 events in 2.7% of participants in the placebo arm. None of these severe TEAEs were considered related to treatment by the investigator. In both study arms, the most common severe TEAE was 'blood potassium increased' (n=7 acoziborole; n=3 placebo) (Table 29). Three of the events reported in the acoziborole group occurred D123, three events occurred on D5

and one event occurred on D31. The events reported on D5 and D31 had a duration of 28-113 days. In the placebo-arm three events of increased potassium was reported on D4, D53 and D121, where the event reported on D4 and had a duration of 4 days. The events of increased potassium are further described in section 6.4.9.2 “clinical chemistry”.

Table 29. Listing of treatment emergent adverse events of Grade 3 or higher – Safety set (SS)

Subject ID/ Age (years)/ Sex	Site	Treatment Group	System Organ Class	Preferred Term	Reported Term	Onset date	Study day	End date	Study day	Duration (days)	Outcome	Severity (grade)	Relation to study drug	Action taken
[redacted]	Bandundu	Acoziborole	Blood And Lymphatic System Disorders	Leukocytosis	Leukocytosis	2022-03-20	5	2022-04-20	36	32	Recovered/Resolved	3	Not Related	None
	Bandundu	Acoziborole	Pregnancy, Puerperium And Perinatal Conditions	Abortion	Abortion	2022-09-20	84	2022-09-20	84	1	Recovered/Resolved	3	Not Related	None
	Bandundu	Placebo	Infections And Infestations	Malaria	Severe Malaria	2022-11-19	93	2022-12-15	119	27	Fatal	5	Not Related	Concomitant Treatment
	Masi Manimba	Acoziborole	Metabolism And Nutrition Disorders	Hypoglycaemia	Hypoglycemia	2022-07-20	127		.	.	Recovering/Resolving	3	Not Related	None
	Masi Manimba	Acoziborole	Investigations	Blood Potassium Increased	Increase In Potassium	2022-03-20	5	2022-07-10	117	113	Recovered/Resolved	3	Not Related	None
			Investigations	Blood Albumin Decreased	Decrease Of Albumin	2022-07-11	118		.	.	Recovering/Resolving	3	Not Related	None
	Masi Manimba	Placebo	Investigations	Blood Potassium Increased	Increase In Potassium	2022-06-28	53	2022-09-13	130	78	Recovered/Resolved	3	Not Related	None
	Masi Manimba	Placebo	Investigations	Aspartate Aminotransferase Increased	Aspartate Aminotransferase Increase	2022-06-20	39	2022-09-12	123	85	Recovered/Resolved	3	Not Related	None
	Masi Manimba	Acoziborole	Investigations	Blood Potassium Increased	Increase In Potassium	2022-10-28	123		.	.	Recovering/Resolving	3	Not Related	None
	Masi Manimba	Acoziborole	Investigations	Blood Potassium Increased	Increase In Potassium	2022-12-14	123		.	.	Recovering/Resolving	3	Not Related	None
	Masi Manimba	Acoziborole	Investigations	Blood Potassium Increased	Increase In Potassium	2023-01-16	123		.	.	Recovering/Resolving	3	Not Related	None
	Masi Manimba	Acoziborole	Investigations	Blood Potassium Increased	Increase In Potassium	2022-10-21	31	2023-01-21	123	93	Recovered/Resolved	3	Not Related	None
	Masi Manimba	Placebo	Investigations	Blood Potassium Increased	Increase In Potassium	2023-05-11	121		.	.	Recovering/Resolving	3	Not Related	None
	Dipumba	Acoziborole	Metabolism And Nutrition Disorders	Hypoalbuminaemia	Hypoalbuminemia	2022-01-03	5	2022-05-02	124	120	Recovered/Resolved	3	Not Related	None
	Dipumba	Acoziborole	Cardiac Disorders	Cardiac Failure	Heart Failure	2022-05-02	31	2022-08-02	123	93	Recovered/Resolved	3	Not Related	Concomitant Treatment
	Dipumba	Acoziborole	Investigations	Blood Potassium Decreased	Decreased Potassium	2022-04-05	4	2022-05-02	31	28	Recovered/Resolved	3	Not Related	None
	Dipumba	Acoziborole	Blood And Lymphatic System Disorders	Anaemia	Anemia	2022-04-13	5	2022-08-08	122	118	Recovered/Resolved	3	Not Related	Concomitant Treatment
	Dipumba	Placebo	Infections And Infestations	Wound Infection	Infected Traumatic Wound On The Big Toe Of The Right Foot	2022-07-03	79	2022-08-01	108	30	Recovered/Resolved	3	Not Related	Concomitant Treatment

[redacted]	Dipumba	Acoziborole	Vascular Disorders	Hypertension	High Blood Pressure	2022-06-01	32		.	.	Not Recovered/Not Resolved	3	Not Related	Concomitant Treatment
	Dipumba	Acoziborole	Investigations	Blood Potassium Increased	Increase In Potassium	2022-10-04	5	2022-10-31	32	28	Recovered/Resolved	3	Not Related	None
	Dipumba	Placebo	Investigations	Blood Potassium Increased	Potassium Increased	2022-12-25	4	2022-12-28	7	4	Recovered/Resolved	3	Not Related	None
	Bagata	Acoziborole	Investigations	Blood Potassium Decreased	Hypokalemia	2023-06-15	121	2023-07-18	154	34	Recovered/Resolved	3	Not Related	None
			Metabolism And Nutrition Disorders	Hypocalcaemia	Hypocalcemia	2023-06-15	121	2023-07-18	154	34	Recovered/Resolved	3	Not Related	None
	Kwamouth	Placebo	Infections And Infestations	Appendicitis	Acute Appendicitis	2022-08-22	8	2022-09-11	28	21	Recovered/Resolved	3	Not Related	Chirurgie
	Dubreka	Placebo	Investigations	Blood Sodium Decreased	Hyponatremia	2022-10-19	162		.	.	Not Recovered/Not Resolved	3	Not Related	Un Peu De Sel Dans La Sauce
	Dubreka	Acoziborole	Investigations	Blood Potassium Increased	Blood Potassium Increase	2022-05-15	5	2022-06-18	39	35	Recovered/Resolved	3	Not Related	Mesures Hygiéno Diététiques
			Vascular Disorders	Hypertension	High Blood Pressure	2022-06-18	39		.	.	Recovering/Resolving	3	Not Related	Concomitant Treatment
	Dubreka	Acoziborole	Investigations	Blood Albumin Decreased	Albumin Decrease	2023-01-10	147		.	.	Not Recovered/Not Resolved	3	Not Related	None
	Dubreka	Acoziborole	Vascular Disorders	Hypertension	High Blood Pressure	2022-09-18	33	2022-10-07	52	20	Recovered/Resolved	3	Not Related	Concomitant Treatment
	Dubreka	Placebo	Vascular Disorders	Hypertension	High Blood Pressure	2022-10-10	40		.	.	Recovering/Resolving	3	Not Related	Concomitant Treatment

The following AEs were considered related to treatment by the investigator in study -04:

Acoziborole arm

All TEAEs reported as related as per Investigator in the acoziborole arm were non-serious. In addition, the 3 serious TEAEs reported in the acoziborole arm were assessed as "not related", by both the Investigator and the Sponsor. The time to onset of the related TEAEs as per the Investigator is mentioned in the Table 30 below.

All related TEAEs as per the Investigator occurred between 1 to 5 days post acoziborole administration.

Table 30 . TEAEs reported by Investigator as related and occurred in relation to the administration of acoziborole treatment (DNDi-OXA-04-HAT)

Participant ID	System Organ Class	Preferred Term	Time to onset (days)
	Nervous System disorders	Headache	2
	Gastro-intestinal disorders	Diarrhea	3
	Musculoskeletal and connective tissue disorders	Muscle spasms	1
	General Disorders and administration site conditions	Fatigue	2
	Gastro-intestinal disorders	Abdominal pain	3
	Gastro-intestinal disorders	Abdominal pain	2
	Gastro-intestinal disorders	Abdominal pain	2

Participant ID	System Organ Class	Preferred Term	Time to onset (days)
	General Disorders and administration site conditions	Pyrexia	1
	Investigations	ECG QT prolonged	5
	Gastro-intestinal disorders	Enteritis	2
	Vascular disorders	Hot flush	1
	General Disorders and administration site conditions	Fatigue	1
	Nervous System disorders	Headache	1
	Gastro-intestinal disorders	Gastrointestinal sounds abnormal	2
	General Disorders and administration site conditions	Fatigue	2
	Metabolism and Nutrition disorders	Decreased appetite	2
	Gastro-intestinal disorders	Abdominal pain	2
	Gastro-intestinal disorders	Nausea	2
	Nervous System disorders	Headache	2
	Nervous System disorders	Headache	2
	Nervous System disorders	Headache	2
	General Disorders and administration site conditions	Pyrexia	1
	Metabolism and Nutrition disorders	Decreased appetite	2
	Psychiatric disorders	Insomnia	2
	Nervous System disorders	Headache	1
	Vascular disorders	Hot flush	2
	Nervous System disorders	Dizziness	2
	Psychiatric disorders	Insomnia	4
	Gastro-intestinal disorders	Nausea	1
	Gastro-intestinal disorders	Abdominal pain	1
	Gastro-intestinal disorders	Nausea	1
	Nervous System disorders	Headache	1
	Gastro-intestinal disorders	Dyspepsia	1
	Nervous System disorders	Headache	2
	Gastro-intestinal disorders	Nausea	3
	Metabolism and Nutrition disorders	Decreased appetite	3
	Nervous System disorders	Headache	2
	Gastro-intestinal disorders	Nausea	1
	General Disorders and administration site conditions	Fatigue	1
	Nervous System disorders	Dizziness	1

Participant ID	System Organ Class	Preferred Term	Time to onset (days)
	Metabolism and Nutrition disorders	Decreased appetite	1
	Gastro-intestinal disorders	Abdominal pain	1
	Nervous System disorders	Headache	1
	Nervous System disorders	Headache	1
	General Disorders and administration site conditions	Fatigue	2
	Nervous System disorders	Dizziness	2
	Nervous System disorders	Headache	1
	Nervous system disorders	Headache	2
	General Disorders and administration site conditions	Fatigue	1
	Metabolism and nutrition disorders	Decreased appetite	1
	General Disorders and administration site conditions	Fatigue	1
	Nervous System disorders	Headache	1
	Metabolism and nutrition disorders	Decreased appetite	2
	Nervous System disorders	Headache	1
	Gastrointestinal disorders	Dysgeusia	2
	Nervous System disorders	Dizziness	1
	Vascular disorders	Hot flush	1
	General Disorders and administration site conditions	Asthenia	1
	General Disorders and administration site conditions	Fatigue	1
	Nervous System disorders	Headache	2
	Gastrointestinal disorders	Vomiting	2
	Nervous System disorders	Headache	2
	Nervous System disorders	Headache	2
	Nervous System disorders	Headache	2
	Nervous System disorders	Headache	2
	Nervous System disorders	Headache	2
	Gastro-intestinal disorders	Abdominal pain	3
	Gastro-intestinal disorders	Abdominal pain	3
	Nervous System disorders	Dizziness	1
	Gastro-intestinal disorders	Abdominal pain	2
	Nervous System disorders	Headache	3
	Gastro-intestinal disorders	Abdominal pain	4

Participant ID	System Organ Class	Preferred Term	Time to onset (days)
	Nervous System disorders	Headache	2
	Gastro-intestinal disorders	Abdominal pain	4
	Nervous System disorders	Headache	4
	Gastro-intestinal disorders	Abdominal pain	4
	Nervous System disorders	Headache	2
	Nervous System disorders	Headache	3
	Gastro-intestinal disorders	Abdominal pain	4
	Nervous System disorders	Headache	3
	Gastro-intestinal disorders	Abdominal pain	3
	Nervous System disorders	Headache	3

Source: DNDi-OXA-04-HAT CSR, Listing 16.2.7.2 : Treatment-related adverse events – Safety set (SS) _ CSR DNDi-OXA-04-HAT B:\OXA-04\Dry_run\output\Listings\Version 2.0_18JUL2024:11:08:02

Abbreviations: ECG, electrocardiogram; **ID,** identifier

Placebo arm

All TEAEs reported as related as per the Investigator in the placebo arm were non-serious. In addition, the 4 serious TEAEs reported in the placebo arm were assessed as "not related", by both the Investigator and the Sponsor. The time to onset of the related TEAEs as per the Investigator is mentioned in the Table 31

below.

All related TEAEs as per the Investigator occurred between 1 to 4 days post-placebo administration.

Table 31 . TEAEs reported by the Investigator as related and occurred in relation to administration of placebo treatment (DNDi-OXA-04-HAT)

Participant ID	System Organ Class	Preferred Term	Time to onset (days)
	Gastro-intestinal disorders	Abdominal pain	1
	Gastro-intestinal disorders	Abdominal pain	1
	Gastro-intestinal disorders	Abdominal pain	1
	Gastro-intestinal disorders	Abdominal pain	1
	Gastro-intestinal disorders	Abdominal pain	3
	Gastro-intestinal disorders	Abdominal pain	3
	Gastro-intestinal disorders	Decreased appetite	2
	Nervous system disorders	Dizziness	2
	General disorders and administration site conditions	Fatigue	2
	General disorders and administration site conditions	Fatigue	1
	General disorders and administration site conditions	Fatigue	2
	General disorders and administration site conditions	Fatigue	1
	General disorders and administration site conditions	Fatigue	1

Participant ID	System Organ Class	Preferred Term	Time to onset (days)
	Nervous system disorders	Headache	4
	Nervous system disorders	Headache	3
	Nervous system disorders	Headache	3
	Nervous system disorders	Headache	4
	Nervous system disorders	Headache	3
	Gastrointestinal disorders	Nausea	1
	Gastrointestinal disorders	Nausea	1
	Cardiac disorders	Tachycardia	2
	Gastrointestinal disorders	Vomiting	1

Source: Listing 16.2.7.2 : Treatment-related adverse events – Safety set (SS) _ CSR DNDi-OXA-04-HAT B:\OXA-04\Dry_run\output\Listings\Version 2.0_18JUL2024:11:08:02

Abbreviation: ID, identifier

Treatment related TEAEs by SOC and PT, overall and by either arm, are described in the table below.

Table 32. Treatment related TEAEs by SOC and PT, overall and by either arm – Safety set (DNDi-OXA-04-HAT)

System Organ Class (SOC) Preferred term (PT)	Acoziborole arm (N = 906)	Placebo arm (N = 300)	Overall (N = 1206)
	n (%) [event]		
At least one IP-related TEAE	**59 (6.5) [82]**	**17 (5.7) [22]**	**76 (6.3) [104]**
SOCs with common[a] and uncommon[b] TEAEs			
Nervous system disorders	**33 (3.6) [34]**	**6 (2.0) [6]**	**39 (3.2) [40]**
Common[a] TEAEs			
Headache	28 (3.1) [28]	5 (1.7) [5]	33 (2.7) [33]
Uncommon[b] TEAEs			
Dizziness	5 (0.6) [5]	1 (0.3) [1]	6 (0.5) [6]
Dysgeusia	1 (0.1) [1]	0	1 (0.1) [1]
Gastrointestinal disorders	**21 (2.3) [24]**	**7 (2.3) [9]**	**28 (2.3) [33]**
Common[a] TEAEs			
Abdominal pain	14 (1.5) [14]	6 (2.0) [6]	20 (1.7) [20]
Uncommon[b] TEAEs			
Nausea	5 (0.6) [5]	2 (0.7) [2]	7 (0.6) [7]
Vomiting	1 (0.1) [1]	1 (0.3) [1]	2 (0.2) [2]
Diarrhoea	1 (0.1) [1]	0	1 (0.1) [1]
Dyspepsia	1 (0.1) [1]	0	1 (0.1) [1]
Enteritis	1 (0.1) [1]	0	1 (0.1) [1]
Gastrointestinal sounds abnormal	1 (0.1) [1]	0	1 (0.1) [1]
General disorders and administration site conditions	**11 (1.2) [11]**	**5 (1.7) [5]**	**16 (1.3) [16]**
Common[a] TEAEs			
Fatigue	8 (0.9) [8]	5 (1.7) [5]	13 (1.1) [13]
Uncommon[b] TEAEs			
Pyrexia	2 (0.2) [2]	0	2 (0.2) [2]
Asthenia	1 (0.1) [1]	0	1 (0.1) [1]
SOCs with uncommon[b] TEAEs only			
Metabolism and nutrition disorders	**6 (0.7) [6]**	**1 (0.3) [1]**	**7 (0.6) [7]**
Decreased appetite	6 (0.7) [6]	1 (0.3) [1]	7 (0.6) [7]
Vascular disorder	**3 (0.3) [3]**	**0**	**3 (0.2) [3]**
Hot flush	3 (0.3) [3]	0	3 (0.2) [3]
Psychiatric disorders	**2 (0.2) [2]**	**0**	**2 (0.2) [2]**
Insomnia	2 (0.2) [2]	0	2 (0.2) [2]
Investigations	**1 (0.1) [1]**	**0**	**1 (0.1) [1]**

SYSTEM ORGAN CLASS (SOC) Preferred term (PT)	Acoziborole arm (N = 906)	Placebo arm (N = 300)	Overall (N = 1206)
		n (%) [event]	
Electrocardiogram QT prolonged	1 (0.1) [1]	0	1 (0.1) [1]
Musculoskeletal and connective tissue disorders	**1 (0.1) [1]**	**0**	**1 (0.1) [1]**
Muscle spasms	1 (0.1) [1]	0	1 (0.1) [1]
Cardiac disorders	**0**	**1 (0.3) [1]**	**1 (0.1) [1]**
Tachycardia	0	1 (0.3) [1]	1 (0.1) [1]

Abbreviations: **IP**, Investigational product; **event,** number of events; **n**, number of participants presenting the event; **N**, total number of participants; **PT**, Preferred term; **SOC**, System organ class; **TEAE**, Treatment emergent adverse event

a Common TEAEs were defined as TEAEs reported in ≥1% of participants overall or in either arm

b Uncommon TEAEs were defined as TEAEs reported in <1% of participants overall or per arm

Note: n (%) [event], number of participants presenting the event (% of participants) [number of events]

5.4.3.3. Clinical pharmacology studies

In study DNDi-OXA-001, at least one TEAE was reported in healthy participants who received various doses of acoziborole 56/102 (54.9%), or placebo 17/26 (65.4%), see Table 33, below.

Table 33. overview of treatment – emergent adverse events in the safety set – study DNDiOXA001

Safety parameter Number of participants (%)	Part I		Part IV	Part VI[a]	Total
	Placebo (N = 26)	Acoziborole (N = 84)	Acoziborole (N = 6)	Acoziborole (N = 12)	Acoziborole (N = 102)
At least one TEAE	**17 (65.4%)**	**43 (51.2%)**	**1 (16.7%)**	**12 (100%)**	**56 (54.9%)**
Mild to moderate TEAE	17 (65.4%)	43 (51.2%)	1 (16.7%)	12 (100%)	56 (54.9%)
Severe TEAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-serious drug-related TEAE	10[b] (38.5%)	30[c] (35.7%)	0 (0%)	12[d] (100%)	42 (40.2%)
Serious drug-related TEAE	0 (0%)	1[e] (0.9%)	0 (0%)	0 (0%)	1 (1.0%)

Abbreviations: **TEAEs**, treatment-emergent adverse event.

a In Part VI, participants received intensive activated charcoal administration: 50 g every 4 hours for 3 days (Day 5 to Day 7).

b Of them, 1 participant had a TEAE probably related to charcoal (unrelated to placebo).

c Of them, 1 participant in the 400 mg cohort had a TEAE possibly related to charcoal (unrelated to acoziborole).

d Most of the drug-related TEAEs were probably related to charcoal.

e One event of asymptomatic hyperthyroidism reported in a participant who received 240 mg of acoziborole.

Among the 6 participants in Part I that received a single dose of 960 mg, four of them reported at least one AE of rash, increased creatinine phosphokinase, insomnia, backpain and headache at mild or moderate intensity. None of the events were considered related to treatment. In part IV were 20 mg acoziborole administered to 6 participants and in Part VI were either 40 or 160 mg acoziborole administered to 6+6 participants.

The AEs reported among the participants that received 960 mg or higher are illustrated in the Table 34 below:

Table 34. Display of related TEAEs by treatment

Dose level	Subject	SOC/PT/Verbatim	AE duration (dd:hh:mm)	Time elapsed from dosing (dd:hh:mm)	Intensity	Relationship to SCYX-7158	Relationship to Activated charcoal	Corrective treatment	Outcome
960 mg	[redacted]	Skin and subcutaneous tissue disorders / Rash pruritic / Macular rash pruritic	06:00:00	02:23:45	Moderate	Unlikely	NA	Yes	Recovered
		Investigations / Blood creatine phosphokinase increased / CPK increase	34:00:07	35:00:44	Moderate	Unlikely	NA	No	Recovered
		Psychiatric disorders / Insomnia / Insomnia	02:17:33	00:19:12	Mild	Unlikely	NA	No	Recovered
		Musculoskeletal and connective tissue disorders / Back pain / Back pain	02:17:00	05:12:45	Mild	Unlikely	NA	No	Recovered
		Nervous system disorders / Headache / Headache	00:12:30	01:02:05	Moderate	Unlikely	NA	Yes	Recovered
		Nervous system disorders / Headache / Headache	00:11:40	02:11:55	Moderate	Unlikely	NA	Yes	Recovered
1000 mg		Investigations / Transaminases Increased / Transaminase Increase	23:00:43	07:23:03	Moderate	Possible	Unrelated	No	Recovered
1200 mg		Gastrointestinal disorders / Abdominal distension / Abdominal bloating	06:02:00	04:10:40	Mild	Unlikely	Possible	No	Recovered
		Gastrointestinal disorders / Abdominal pain upper / Epigastralgia	01:16:00	01:07:30	Mild	Unlikely	Unrelated	No	Recovered
		Nervous system disorders / Dizziness postural / Dizziness in standing position	00:00:18	00:01:07	Moderate	Unlikely	Unrelated	No	Recovered
		Nervous system disorders / Loss of consciousness / Loss of consciousness	00:00:00	00:01:10	Moderate	Unlikely	Unrelated	No	Recovered
		Metabolism and nutrition disorders / Decreased appetite / Loss of appetite	10:00:00	00:23:05	Mild	Possible	Unrelated	No	Recovered

* reported on December 3rd, 2013 as AE and then became SAE on January 6th, 2014

In study DNDi-OXA-03, six participants received 960 mg acoziborole and reported 13 AEs. Headache was the most reported PT (n=4) of which two were considered related to treatment. Headache is proposed to be included as ADR in the product information.

Study DNDi-OXA-07-HAT included 19 participants that received 960 mg acoziborole to which subsequently midazolam and dextromethorphan were administered. The reported TEAEs occurred after administration of dextromethorphan and midazolam. No additional safety information on acoziborole was obtained from this study, and all reported TEAEs were considered related to the other treatments included in the study.

5.4.3.4. Adverse drug reactions

The causality of TEAEs reported by Investigators as related in study DNDi-OXA-02-HAT was analyzed by the Sponsor (Drug for Neglected Diseases initiative - DNDi), using the Bradford-Hill criteria[12] for causality, the guidance on clinical trial safety of the Council for International Organizations of Medical Sciences (CIOMS)[13], and the guidance of the European Commission[14]. All TEAEs reported as related as per the Investigator occurred from Day 1 to Day 4 post acoziborole administration.

Whilst the underlying mechanism of headache is unclear, the observed consistency across studies supports a causal relationship. The relatively low number of headaches reported as related in DNDi-OXA-02-HAT may be due to the high prevalence of headaches in this population and the inherent difficulty in distinguishing headaches due to the disease from those due to the lumbar puncture and those related to acoziborole.

According to the Applicant, there was insufficient evidence to support a causal relationship for all other TEAEs reported by the Investigators as related in study DNDi-OXA-02-HAT. The TEAEs were mostly confounded by the underlying disease or explained by comorbidities. Most TEAEs reported in study

[12] UMC. (Uppsala Monitoring Centre). Bradford-Hill Criteria. Available from: https://edit.who-umc.org/signal-management/bradford-hill-criteria/. Last modified on: 9 March 2025. Last accessed on: 07 January 2026.
[13] CIOMS. (Council for International Organizations of Medical Sciences). Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI. CIOMS, Geneva, Switzerland, 2005. Available from: https://cioms.ch/publications/product/management-of-safety-information-from-clinical-trials-report-of-cioms-working-group-vi. Last accessed on: 07 January 2026.
[14] EC. (European Commission). A guideline on summary of product characteristics (SmPC). September 2009. Revision 2. Available from: https://health.ec.europa.eu/document/download/6a043dea-7d0f-4252-947b-cef58f53d37e_en. Last accessed on: 07 January 2026

DNDi-OXA-02-HAT were reported in study DNDi-OXA-04-HAT with similar frequencies in participants randomized to acoziborole and placebo, or in very low numbers, or not at all.

The Applicant has proposed to include the AEs that were considered related to acoziborole in the pivotal study DNDi-OXA-02 as ADRs in the SmPC. The frequency calculation was as follows:

- Common ADRs

Pyrexia (10/208 [4.8%]), Asthenia (6/208 [2.9%]), Decreased appetite (4/208 [1.9%]), Tremor (3/208 [1.4%]). According to the investigator 2/208 participants experienced headache related to treatment in study -02, however, headache was reported in 25% of the participants in that study. In study -04 headache was more frequent reported among the participants receiving study drug (acoziborole 5,8%; placebo 2,7%), and also a higher frequency was considered related to treatment according to the investigator (3.1% acoziborole; 1.7% placebo).

- Uncommon ADRs

Dyskinesia and Abdominal pain (each ADR occurred in 2/208 [0.96%]). Chills, Dizziness, Nausea, Vomiting and Pruritus (each ADR occurred in 1/208 [0.5%]). This results are supported by the data presented in study -04.

Table 35. Summary of ADRs proposed for inclusion by the applicant in the SmPC

Metabolism and Nutrition Disorders		Link to data*
Common	Decreased appetite	Study DNDi-OXA-02, related AE
Nervous System Disorders		
Common	Tremor, Headache	Study DNDi-OXA-02, related AE, Table 25
Uncommon	Dyskinesia, Dizziness	DNDi-OXA-02-HAT, related AE.
Gastrointestinal Disorders		
Uncommon	Abdominal pain, Nausea, Vomiting	DNDi-OXA-02-HAT, related AE
Skin and Subcutaneous Tissue Disorders		
Uncommon	Pruritus	DNDi-OXA-02-HAT, related AE,
General Disorders and Administration Site Conditions		
Common	Pyrexia, Asthenia	DNDi-OXA-02-HAT, related AE, Table 25
Uncommon	Chills	DNDi-OXA-02-HAT, related AE,
Investigations		
Very common	Electrocardiogram QT shortened	DNDi-OXA-02-HAT, related AE, section "electrocardiogram"

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Table 17: Adverse events of special interest, SAEs and deaths (full analysis set)

5.4.4.1. AESIs

No AESIs were defined for any of the clinical or pharmacological studies.

5.4.4.2. SAEs

Participants with g-HAT (study DNDi-OXA-02-HAT)

During the reporting period 27 TEAEs were reported as serious in 21/208 (10.1%) participants (see Table 36, below).

Table 36. overview of all serious TEAS by system organ class and preferred term (treated set)-Study DNDi-OXA-02-HAT

SOC/PT Number of participants (%) *number of events*	Early and Intermediate stage (N = 41)	Late stage (N = 167)	Total (N = 208)
At least one serious TEAE	**3 (7.3%) *4***	**18 (10.8%) *23***	**21 (10.1%) *27***
Infections and infestations	**1 (2.4%) *1***	**8 (4.8%) *9***	**9 (4.3%) *10***
Malaria	0 (0.0%) *0*	2 (1.2%) *2*	2 (0.96%) *2*
Appendicitis	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Extrapulmonary tuberculosis	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Gastroenteritis	0 (0.0%) *0*	1 (0.6%) *2*	1 (0.5%) *2*
Puerperal infection	1 (2.4%) *1*	0 (0.0%) *0*	1 (0.5%) *1*
Systemic infection	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Thyphoid fever	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Upper respiratory tract infection	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Psychiatric disorders	**0 (0.0%) *0***	**6 (3.6%) *7***	**6 (2.9%) *7***
Acute psychosis	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Bipolar I disorder	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Brief psychotic disorder with marked stressors	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Major depression	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Mania	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Organic brain syndrome	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Suicide attempt	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Gastrointestinal disorders	**1 (2.4%) *1***	**1 (0.6%) *1***	**2 (0.96%) *2***
Abdominal adhesions	1 (2.4%) *1*	0 (0.0%) *0*	1 (0.5%) *1*
Inguinal hernia	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Nervous system disorders	**0 (0.0%) *0***	**2 (1.2%) *2***	**2 (0.96%) *2***
Guillain-Barre syndrome	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Intracranial pressure increased	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Respiratory, thoracic and mediastinal disorders	**0 (0.0%) *0***	**2 (1.2%) *2***	**2 (0.96%) *2***
Acute pulmonary edema	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Choking	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Injury, poisoning and procedural complications	**0 (0.0%) *0***	**1 (0.6%) *1***	**1 (0.5%) *1***
Poisoning	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*
Pregnancy, puerperium and perinatal conditions	**1 (2.4%) *2***	**0 (0.0%) *0***	**1 (0.5%) *2***
Postpartum hemorrhage	1 (2.4%) *1*	0 (0.0%) *0*	1 (0.5%) *1*
Umbilical cord prolapse	1 (2.4%) *1*	0 (0.0%) *0*	1 (0.5%) *1*
Reproductive system and breast disorders	**0 (0.0%) *0***	**1 (0.6%) *1***	**1 (0.5%) *1***
Ovarian cyst	0 (0.0%) *0*	1 (0.6%) *1*	1 (0.5%) *1*

Abbreviations: **PT**, preferred term; **SOC**, system organ class; **TEAE**, treatment-emergent adverse event.

The most common serious TEAEs (in >2% of participants per SOC overall) were reported in the SOCs of infections and infestations (9/208 [4.3%] participants overall), and psychiatric disorders (6/208 [2.9%] participants overall; all with late-stage g-HAT). Of the 27 serious TEAEs, 7 events were of mild or moderate severity, and 20 events were severe, life-threatening or fatal. No serious TEAEs were considered drug-related as assessed by both the Investigator and the Sponsor, and all non-fatal serious TEAEs had been resolved by EOS, but in 1 case with sequelae (Participant described below).

Most participants (n=19) reported serious AEs after the hospitalization period of the study, Table 37

Table 37. Serious TEAE occurred during post-hospitalizatin by MedDRA SOC and PT – Treated set by stage of disease and overall

	HAT stage											
	Stage 1 (N=18)			Intermediate stage (N=23)			Stage 2 (N=167)			Total (N=208)		
Primary System Organ Class / Dictionary-Derived Term	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat	Nb AE	Nb pat	% pat
ANY ADVERSE EVENTS	1	1	5.6	3	2	8.7	19	16	9.6	23	19	9.1
Gastrointestinal disorders	1	1	5.6	.	.	.	1	1	0.6	2	2	1.0
- Abdominal adhesions	1	1	5.6	.	.	.	.	.	.	1	1	0.5
- Inguinal hernia	.	.	.	.	.	.	1	1	0.6	1	1	0.5
Infections and infestations	.	.	.	1	1	4.3	8	7	4.2	9	8	3.8
- Appendicitis	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Extrapulmonary tuberculosis	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Gastroenteritis	.	.	.	.	.	.	2	1	0.6	2	1	0.5
- Malaria	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Puerperal infection	.	.	.	1	1	4.3	.	.	.	1	1	0.5
- Systemic infection	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Typhoid fever	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Upper respiratory tract infection	.	.	.	.	.	.	1	1	0.6	1	1	0.5
Injury, poisoning and procedural complications	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Poisoning	.	.	.	.	.	.	1	1	0.6	1	1	0.5
Pregnancy, puerperium and perinatal conditions	.	.	.	2	1	4.3	.	.	.	2	1	0.5
- Postpartum haemorrhage	.	.	.	1	1	4.3	.	.	.	1	1	0.5
- Umbilical cord prolapse	.	.	.	1	1	4.3	.	.	.	1	1	0.5
Psychiatric disorders	.	.	.	.	.	.	6	5	3.0	6	5	2.4
- Acute psychosis	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Brief psychotic disorder with marked stressors	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Major depression	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Mania	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Organic brain syndrome	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Suicide attempt	.	.	.	.	.	.	1	1	0.6	1	1	0.5
Reproductive system and breast disorders	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Ovarian cyst	.	.	.	.	.	.	1	1	0.6	1	1	0.5
Respiratory, thoracic and mediastinal disorders	.	.	.	.	.	.	2	2	1.2	2	2	1.0
- Acute pulmonary oedema	.	.	.	.	.	.	1	1	0.6	1	1	0.5
- Choking	.	.	.	.	.	.	1	1	0.6	1	1	0.5

The following 4 serious AEs occurred up to Day 15:

Adult participant experienced increased intracranial pressure on Day 7 which resolved post-hospitalization on Day 24. On Day 25, the participant had a serious TEAE of poisoning, which led to death the same day (see section death).

Adult participant experienced progressive ascending peripheral neuropathy (registered as PT Guillain-Barré syndrome) on Day 10 which resulted in death on Day 38 (see section death). She also experienced asphyxia on food aspiration on Day 24.

Adult participant with a history of behaviour disorders such as aggressiveness, nervousness, manic depression, lagorrhea and insomnia. On Day 15 he experienced psychiatric disorder type manic depressive (Bipolar I disorder) and received treatment at a psychiatric unit and recovered two months later.

Adult participant got fever on D13 and was diagnosed with malaria on D15. He recovered after treatment.

The serious events of CTCAE Grade 4 (life-threatening) reported in 3 participants is presented below.

Adult participant with late-stage g-HAT experienced a serious TEAE of "outburst of delirious episodes" (PT: brief psychotic disorder with marked stressors) and required hospitalization on Day 88, ie, 87 days after having received acoziborole. Following treatment, the event resolved with sequelae nearly 18 months later. The event, as assessed by the Investigator and the Sponsor, was considered unrelated to acoziborole.

Adult participant with late-stage g-HAT experienced serious TEAEs of major depression and suicide attempt on Day 96, ie, 95 days after having received acoziborole. Following antidepressant treatment, the event was resolved nearly 2 months later. Both events, as assessed by the Investigator and the Sponsor, were considered unrelated to acoziborole.

Adult participant with intermediate-stage g-HAT experienced a serious TEAE of umbilical cord prolapse during delivery (life-threatening) on Day 326, ie, 325 days after having received acoziborole. This participant also experienced a serious TEAE of postpartum hemorrhage (severe) on the same day. Both events had resolved following treatment on Day 336 and were considered unrelated to acoziborole, as assessed by the Investigator and the Sponsor.

Other study participant populations (study DNDi-OXA-04-HAT)

In study all the 7 serious TEAEs reported in the study occurred after hospitalization (ie, after Day 5), Table 38. None of these events were considered as drug-related.

Table 38. Listing of Serious treatment emergent adverse events – Safety set (SS)

Subject ID/ Age (years)/ Sex	Site	Treatment Group	System Organ Class	Preferred Term	Reported Term	Onset date	Study day	Outcome date	Study day	Duration (days)	Outcome	Severity (grade)	Relation to study drug	Action taken
[redacted]	Bandundu	Acoziborole	Pregnancy, Puerperium And Perinatal Conditions	Abortion	Abortion	2022-09-20	84	2022-09-20	84	1	Recovered/Resolved	3	Not Related	None
	Bandundu	Placebo	Infections And Infestations	Malaria	Severe Malaria	2022-12-03	107	2022-12-15	119	13	Fatal	5	Not Related	Concomitant Treatment
	Masi Manimba	Acoziborole	Reproductive System And Breast Disorders	Uterine Prolapse	Uterine Prolapse	2023-04-10	24	2023-04-23	37	14	Recovered/Resolved	2	Not Related	Chirurgie Majeure(Hysteropexie)
	Dipumba	Placebo	Infections And Infestations	Wound Infection	Infected Traumatic Wound On The Big Toe Of The Right Foot.	2022-07-14	90	2022-08-01	108	19	Recovered/Resolved	3	Not Related	Concomitant Treatment
	Dipumba	Acoziborole	Reproductive System And Breast Disorders	Vaginal Haemorrhage	Vaginal Hemorrhage	2023-04-21	121	2023-05-03	133	13	Recovered/Resolved	2	Not Related	Concomitant Treatment
	Bagata	Placebo	Surgical And Medical Procedures	Abortion Induced	Induced Abortion	2022-11-18	87	2022-11-24	93	7	Recovered/Resolved	2	Not Related	None
	Kwamouth	Placebo	Infections And Infestations	Appendicitis	Acute Appendicitis	2022-08-28	14	2022-09-11	28	15	Recovered/Resolved	3	Not Related	Chirurgie

Six of the 7 serious TEAEs resolved at EOS. The event of malaria had a fatal outcome (see section death). The following serious TEAEs reported in the acoziborole group:

Adult participant had a uterine prolapse on Day 23. The event was of moderate intensity, the participant underwent major surgery and recovered from the event.

Adult participant experienced moderate vaginal haemorrhage on Day 120 days. The participant recovered after treatment.

Adult participant experienced abortion on Day 83 (see section pregnancy).

Six additional SAEs were reported in 5 participants after the study reporting period (ie, after the EOS visit at Month 4): all 6 events were linked to the outcome of pregnancy and are further described in the pregnancy part of this AR. These SAEs were reported in 4 participants in the acoziborole arm (for 1 participant the SAE was fatal for the fetus), and in 1 participant in the placebo arm.

Clinical pharmacology studies

In study DNDiOXA001, 1 serious AE of low TSH value was reported in one participant:

Adult participant was identified with low TSH value 67 days after recieving acoziborole at 240 mg with charcoal. A second control 28 days later showed decreased TSH and elevation of thyroxin and free triiodothyronine. The participant had no clinical signs at any time point. The last control that occurred 55 days later indicated a normalization of hyroid hormones and TSH. The event was considered possibly related to acoziborole by the investigator and the sponsor.

No SAEs were reported in studies DNDi-OXA-03-HAT and DNDi-OXA-07-HAT

5.4.4.3. Deaths

Participants with g-HAT (study DNDi-OXA-02-HAT)

There were 4 deaths reported (1.9%), all in participants with late-stage g-HAT (Table 39). None of the deaths were considered related to acoziborole or HAT as assessed by the Investigator and the Sponsor. Before administration of treatment, one fatal SAE occurred in a male participant during screening due to an acute fulminant hepatitis. The narratives of the four deaths are summarized in the efficacy section.

Table 39. Summary of TEAEs that led to death – Study DNDi-OXA-02-HAT

Participant ID	Preferred term	Causality[a]	Start date - End date[b]
[redacted]	Guillain Barré syndrome	Unrelated	Day 10 – Day 38
	Poisoning	Unrelated	Day 25 – Day 25
	Extrapulmonary tuberculosis	Unrelated	Day 224 – Day 224
	Acute pulmonary edema	Unrelated	Day 388 – Day 392

Abbreviations: **ID**, identification; **TEAE**, treatment-emergent adverse event.
a As assessed by both the Investigator and the Sponsor
b Day 1 was the day of treatment

Other study participant populations

No event of death was reported in the acoziborole group. In study DNDi-OXA-04-HAT, one death due to severe malaria infection was reported in the placebo arm.

Elderly participant, a TEAE of malaria was reported 92 days after placebo administration and considered not drug-related. This TEAE became serious 2 weeks later and required hospitalization. The participant was treated for the SAE of complicated malaria with artemisinin, but the evolution was not favorable. The family refused further treatment, and the participant was voluntarily discharged from the referral health center against medical advice and died on Day 118

Clinical pharmacology studies

No deaths were reported in the pharmacology studies DNDiOXA001, DNDi-OXA-03-HAT and DNDi-OXA-07-HAT.

5.4.5. Discontinuation due to adverse events

Participants with g-HAT (Study DNDi-OXA-02)

Of the 208 treated patients, 201 patients (96.6%) completed the trial: all 41 patients (100.0%) with early- or intermediate-stage HAT and 160 patients (95.8%) with late-stage HAT. The remaining 7/208 patients (3.4%), all with late-stage HAT, discontinued the trial due to: death (4 patients; deaths not related to study drug or HAT), loss to follow-up (1 patient) and use of rescue therapy (2 patients). None of the participants discontinued the study due to adverse events.

Other study population (Study DNDi-OXA-04)

Of the 1208 randomized and treated participants, a total of 1196 (99%) participants completed the study (i.e. attended the EoS visit at Month 4).

• Acoziborole arm: of the 907 participants randomized to this arm, 898 (99%) completed the study. The reasons for early discontinuation were lost to follow-up (for 7 [0.8%] participants) and consent withdrawal (for 2 [0.2%] participants)

• Placebo arm: of the 301 participants randomized to this arm, 298 (99%) completed the study. The reasons for early discontinuation were death, lost to follow-up and consent withdrawal, each reported in 1 (0.3%) participant.

None of the participants discontinued the study due to adverse events.

Clinical pharmacology studies

None of the participants discontinued the study due to adverse events.

5.4.6. Safety in special populations

Table 40. TEAEs by seriousness, SOC, and PT and study in participants aged 65 years and older exposed to acoziborole

TEAEs in participants 65 years and older	DNDi-OXA-02-HAT (N = 3)	DNDi-OXA-04-HAT (N = 67)	Total (N = 70)
	n (%) [event]		
Participants with at least one TEAE	**2 (66.7) [3]**	**20 (29.9) [32]**	**22 (31.4) [35]**
Participants with at least one Serious TEAE	**0**	**0**	**0**
TEAEs by SOC and PT			
Blood and lymphatic system disorders	**0**	**1 (1.5) [1]**	**1 (1.4) [1]**
Anaemia	0	1 (1.5) [1]	1 (1.4) [1]
Gastrointestinal disorders	**0**	**3 (4.5) [3]**	**3 (4.3) [3]**
Diarrhoea	0	1 (1.5) [1]	1 (1.4) [1]
Enteritis	0	1 (1.5) [1]	1 (1.4) [1]
Gingival Pain	0	1 (1.5) [1]	1 (1.4) [1]
General disorders and administration site conditions	**0**	**1 (1.5) [1]**	**1 (1.4) [1]**
Pyrexia	0	1 (1.5) [1]	1 (1.4) [1]

TEAEs in participants 65 years and older	DNDi-OXA-02-HAT (N = 3)	DNDi-OXA-04-HAT (N = 67)	Total (N = 70)
	n (%) [event]		
Hepatobiliary disorders	**0**	**2 (3.0) [2]**	**2 (2.9) [2]**
Hepatomegaly	0	2 (3.0) [2]	2 (2.9) [2]
Infections and infestations	**0**	**9 (13.4) [10]**	**9 (12.9) [10]**
Malaria	0	2 (3.0) [2]	2 (2.9) [2]
Conjunctivitis	0	1 (1.5) [1]	1 (1.4) [1]
Dysentery	0	1 (1.5) [1]	1 (1.4) [1]
Erysipelas	0	1 (1.5) [1]	1 (1.4) [1]
Fungal Infection	0	1 (1.5) [1]	1 (1.4) [1]
Gastroenteritis	0	1 (1.5) [1]	1 (1.4) [1]
Respiratory Tract Infection	0	1 (1.5) [1]	1 (1.4) [1]
Skin Infection	0	1 (1.5) [1]	1 (1.4) [1]
Wound Infection	0	1 (1.5) [1]	1 (1.4) [1]
Injury, poisoning and procedural complications	**1 (33.3) [1]**	**0**	**1 (1.4) [1]**
Procedural Pain	1 (33.3) [1]	0	1 (1.4) [1]
Investigations	**0**	**4 (6.0) [4]**	**4 (5.7) [4]**
Blood Potassium Increased	0	3 (4.5) [3]	3 (4.3) [3]
Platelet Count Decreased	0	1 (1.5) [1]	1 (1.4) [1]
Metabolism and nutrition disorders	**0**	**2 (3.0) [2]**	**2 (2.9) [2]**
Decreased Appetite	0	2 (3.0) [2]	2 (2.9) [2]
Musculoskeletal and connective tissue disorders	**0**	**1 (1.5) [1]**	**1 (1.4) [1]**
Back Pain	0	1 (1.5) [1]	1 (1.4) [1]
Nervous system disorders	**1 (33.3) [1]**	**3 (4.5) [3]**	**4 (5.7) [4]**
Headache	1 (33.3) [1]	3 (4.5) [3]	4 (5.7) [4]
Respiratory, thoracic and mediastinal disorders	**1 (33.3) [1]**	**1 (1.5) [1]**	**2 (2.9) [2]**
Cough	1 (33.3) [1]	0	1 (1.4) [1]
Rhinitis Allergic	0	1 (1.5) [1]	1 (1.4) [1]
Skin and subcutaneous tissue disorders	**0**	**1 (1.5) [1]**	**1 (1.4) [1]**
Pruritus	0	1 (1.5) [1]	1 (1.4) [1]
Vascular disorders	**0**	**3 (4.5) [3]**	**3 (4.3) [3]**
Hypertension	0	3 (4.5) [3]	3 (4.3) [3]

Abbreviations: **PT**, preferred term; **TEAE**, treatment-emergent adverse event; **SOC,** system organ class
Note: n (%) [event], number of participants presenting the event (% of participants) [number of events]

Table 41. Renal function at baseline by study (acoziborole-exposed participants only)

Renal function test category at baseline	DNDi-OXA-03-HAT (N = 6)	DNDi-OXA-07-HAT (N = 20)	DNDiOXA001 (N = 96)	DNDi-OXA-02-HAT (N = 208)	DNDi-OXA-04-HAT (N = 906)	Total n/N (%)
			n (%)			
Glomerular filtration rate (GFR)						
> 90	5 (83.3)	20 (100)	-	-	-	25/26 (96.2)
60 to 89	1 (16.7)	0	-	-	-	1/26 (3.8)
				Serum creatinine		
Up to ULN	-	-	81 (84.4)	194 (93.3)	867 (95.7)	1142/1210 (94.4)
> ULN to 1.5 x ULN	-	-	15 (15.6)	13 (6.3)	38 (4.2)	66/1210 (5.5)
> 1.5 to 3.0 x ULN	-	-	0	1 (0.5)	1 (0.1)	2/1210 (0.2)

Abbreviations: n, number of participants presenting laboratory abnormality; **N**, total number of participants; **GFR,** glomerular filtration rate; **ULN**, upper limit of normal

Table 42. Hepatic function at baseline by study (acoziborole-exposed participants only)

Hepatic function parameters and category	DNDi-OXA-03-HAT (N = 6)	DNDi-OXA-07-HAT (N = 20)	DNDiOXA 001 (N = 96)	DNDi-OXA-02-HAT (N = 208)	DNDi-OXA-04-HAT (N = 906)	Total (N = 1236)
				n (%)		
Total bilirubin						
> ULN to 1.5 x ULN	0	1 (5.0)	7 (7.3)	0	11 (1.2)	19 (1.5)
> 1.5 to 3.0 x ULN	0	0	3 (3.1)	0	0	3 (0.2)
> 3.0 x ULN	0	0	0	0	0	0
Serum albumin						
< LLN to 3.0 g/dl or 30 g/L	0	0	0	0	380 (41.9)	380 (30.7)
< 3.0 g/dl or 30 g/L to 2.0 g/dl or 20 g/L	0	0	0	0	220 (24.3)	220 (17.8)
< 2.0 g/dl or 20 g/L	0	0	0	208 (100)	9 (1.0)	217 (17.6)
PT INR						
> 1.2 to 1.5	-	-	5 (5.2)	-	-	5 (5.2)
> 1.5 to 2.5	-	-	1 (1.0)	-	-	1 (1.0)
> 2.5	-	-	0	-	-	0

Hepatic function parameters and category	DNDi-OXA-03-HAT (N = 6)	DNDi-OXA-07-HAT (N = 20)	DNDiOXA 001 (N = 96)	DNDi-OXA-02-HAT (N = 208)	DNDi-OXA-04-HAT (N = 906)	Total (N = 1236)
			n (%)			

Abbreviations: INR, International Normalized Ratio; **LLN**, Lower Limit of Normal; **PT**, prothrombin time; **ULN**, Upper Limit of Normal
Participants were not assessed as per the Child-Pugh criteria. Therefore, no information about the safety profile of acoziborole in patients with Child-Pugh category B or C is available

Table 43. TEAEs by seriousness, SOC, and PT in pregnant women exposed to acoziborole by study

TEAEs in pregnant women	DNDi-OXA-02-HAT (N = 4)	DNDi-OXA-04-HAT (N = 5)	Total (N = 9)
		n (%) [event]	
Subjects with at least one TEAE	**3 (75.0) [8]**	**4 (80.0) [9]**	**7 (77.8) [17]**
Subjects with at least one Serious TEAE	**2 (50.0) [3]**	**4 (80.0) [4]**	**6 (66.7) [7]**
Fatal	0	0	0
Hospitalization/ prolongation of hospitalization	1 (25.0) [1]	1 (20.0) [1]	2 (22.2) [2]
Life-threatening	1 (25.0) [2]	1 (20.0) [1]	2 (22.2) [3]
Disability/ incapacity	0	0	0
Congenital anomaly/birth defect	0	0	0
Other (medically significant)	0	2 (40.0) [2]	2 (22.2) [2]
TEAEs by SOC and PT			
Blood and lymphatic system disorders	**0**	**1 (20.0) [1]**	**1 (11.1) [1]**
Anaemia	0	1 (20.0) [1]	1 (11.1) [1]
Gastrointestinal disorders	**0**	**1 (20.0) [1]**	**1 (11.1) [1]**
Gastritis	0	1 (20.0) [1]	1 (11.1) [1]
Infections and infestations	**1 (25.0) [1]**	**2 (40.0) [3]**	**3 (33.3) [4]**
Genital infection	0	1 (20.0) [1]	1 (11.1) [1]
Malaria	0	1 (20.0) [1]	1 (11.1) [1]
Puerperal Infection	1 (25.0) [1]	0	1 (11.1) [1]
Upper Respiratory Tract Infection	0	1 (20.0) [1]	1 (11.1) [1]
Musculoskeletal and connective tissue disorders	**1 (25.0) [1]**	**0**	**1 (11.1) [1]**
Back pain	1 (25.0) [1]	0	1 (11.1) [1]
Nervous system disorders	**1 (25.0) [3]**	**0**	**1 (11.1%) [3]**
Headache	1 (25.0) [3]	0	1 (11.1) [3]
Pregnancy, puerperium and perinatal conditions	**1 (25.0) [2]**	**4 (80.0) [4]**	**5 (55.6) [6]**
Abortion	0	1 (20.0) [1]	1 (11.1) [1]
Cephalo-pelvic disproportion	0	1 (20.0) [1]	1 (11.1) [1]
Foetal distress syndrome	0	1 (20.0) [1]	1 (11.1) [1]

TEAEs in pregnant women	DNDi-OXA-02-HAT (N = 4)	DNDi-OXA-04-HAT (N = 5)	Total (N = 9)
		n (%) [event]	
Postpartum Haemorrhage	1 (25.0) [1]	0	1 (11.1) [1]
Premature rupture of membranes	0	1 (20.0) [1]	1 (11.1) [1]
Umbilical Cord Prolapse	1 (25.0) [1]	0	1 (11.1) [1]
Respiratory, thoracic and mediastinal disorders	**1 (25.0) [1]**	**0**	**1 (11.1) [1]**
Cough	1 (25.0) [1]	0	1 (11.1) [1]

Abbreviations: **PT**, preferred term; **TEAE**, treatment-emergent adverse event; **SOC,** system organ class
Note: n (%) [event], number of participants presenting the event (% of participants) [number of events]

5.4.6.1. Use in Pregnancy and Breastfeeding

The use of acoziborole has not been studied in pregnant or breastfeeding women. However, there were cases of pregnancies in studies DNDi-OXA-02-HAT and DNDi-OXA-04-HAT.

Pregnancy

The pregnancies reported in study -02 and -04 are summarized in Table 44 below.

Table 44. Summary of pregnancy in phase II/III clinical triales

Participant ID g-HAT stage	Pregnancy			Complication			
	Start date	Fetus exposure	Outcome	Start date	PT	Seriousness	Drug relatedness
Study DNDi-OXA-02-HAT							
[redacted] Late stage	D-30	Yes	Normal vaginal delivery Healthy newborn in good general condition, and healthy infant with normal development at 24 months of age	-	-	-	-
[redacted] Early stage	D86	No	Normal vaginal delivery Healthy newborn in good general condition, and healthy infant with delayed physical and motor development at 24 months of age, due to malnutrition	-	-	-	-
[redacted] Intermediate stage	D56	Yes	Stillborn	D326	Postpartum hemorrhage (serious TEAE) Umbilical cord prolapse (serious TEAE)	Life-threatening Hospitalization	Unrelated
[redacted] Late stage	>D31	Yes	Normal vaginal delivery Healthy newborn in good general condition, and healthy infant with normal development at 24 months of age	-	-	-	-
[redacted] Late stage	D123	No	Delivery by cesarean section Healthy newborn in good general condition, and healthy infant with normal development at 24 months of age	D405	Neonatal asphyxia (SAE)[a]	Fatal to the newborn	Unrelated
[redacted] Intermediate stage	D-7	Yes	Normal vaginal delivery Newborn in bad condition, and died 2 days later	D265	Puerperal infection (serious TEAE) and sepsis in the newborn (SAE)[a]	Fatal to the newborn	Unrelated
[redacted] Late stage	D141	No	Normal vaginal delivery Healthy newborn in good general condition, and healthy infant with normal development at 24 months of age	-	-	-	-
Participant ID g-HAT stage	**Pregnancy**			**Complication**			
	Start date	**Fetus exposure**	**Outcome**	**Start date**	**PT**	**Seriousness**	**Drug relatedness**
Study DNDi-OXA-04-HAT							
Acoziborole arm							
[redacted]	D-9	Yes	Abortion	D84	Abortion (serious TEAE)	Other medically important event	Unrelated[b]
	D74	No	Normal vaginal delivery Healthy newborn in good general condition and healthy infant with normal development at 12 months of age	-	-	-	-
	D2	Yes	Delivery by lower cesarean section Healthy newborn in good general condition and healthy infant with normal development at 19 months of age	D298	Cephalopelvic disproportion (SAE)[a]	Life-threatening Hospitalization	Unrelated
	About M2	Yes	Delivery by lower cesarean section Healthy newborn in good general condition, and healthy infant with normal development at 18 months of age	D310	Fetal distress syndrome (SAE)[a]	Hospitalization Other medically important event	Unrelated
	D92	No	Normal vaginal delivery Healthy newborn in good general condition and healthy infant with normal development at 20 months of age	-	-	-	-
	D93	No	Umbilical cord prolapse (not pulsative) and subsequent spontaneous expulsion of the fetus by normal vaginal delivery Fetal death due to umbilical cord prolapse and prematurity	D274	Umbilical cord prolapse (SAE)[a] Vaginal bleeding (SAE)[a]	Hospitalization Other medically important event Fatal to the fetus	Unrelated
	D21	Yes	Normal vaginal delivery Healthy newborn in good general condition and healthy infant with normal development at 18 months of age	-	-	-	-
	D1	Yes	Delivery by cesarean section Healthy newborn in good general condition and healthy infant with normal development at 16 months of age	D301	Premature rupture of membrane (serious TEAE)	Other medically important condition	Unrelated
Study DNDi-OXA-04-HAT							
Placebo arm							
[redacted]	D75	-	Spontaneous abortion	NA	Abortion spontaneous (SAE)[a]	Hospitalization (D185) Other medically important condition	Unrelated
	D-19	-	Medically induced abortion	D87	Abortion induced (serious TEAE)	Other medically important event	Unrelated
	D-22	-	Normal vaginal delivery Healthy newborn in good general condition and healthy infant with normal development at 18 months of age	-	-	-	-

Abbreviations: **D**, day; **g-HAT**, human African trypanosomiasis due to *Trypanosomia brucei gambiense*; **ID**, identification number; **M**, month; **NA**, not available; **PT**, preferred term; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event.

a These SAEs reported after the end of study visit were not included in the listing of serious TEAEs.

b Probably induced and related to the use of traditional plants and other unknown drugs.

Source: 5.3.5.2 Study DNDi-OXA-02-HAT Section 12.5.7, and 5.3.5.4 study DNDI-OXA-04-HAT Table 21.

Study DNDi-OXA-02-HAT

Seven pregnancies were reported of which 5 of them resulted in healthy newborns. Narratives for the two other cases are presented below.

Adult female participant with intermediate-stage HAT, the pregnancy was revealed to have started 55 days after exposure to the study drug (i.e., Day 56). She has had 5 pregnancies before. No concomitant medication was reported. At the Month 3 visit, the patient tested positive for pregnancy. On Day 324 the patient consulted the health centre of the village for lumbohypogastralgia (labour pains), and she was diagnosed with labour in breech position with rupture of the amniotic sac. Foetal heart beats were present. Transfer of the patient to hospital was indicated but the patient remained in the health centre for observation upon relative's decision (due to the distance to hospital estimated to be 45 km). On Day 325, labour remained stationary with the feet of the foetus at the vulva and umbilical cord prolapse. The midwife administered the patient with oxytocin (10 IU once IM) to speed up the labour. Caesarian section was not performed due to lack of technical capacity. After some laborious obstetric manoeuvres, she gave birth to a male newborn of 3.5 kg (unknown height) with an APGAR score of 0/10 after 1, 5 and 10 min, via breech eviction. Neonatal resuscitation was unsuccessful. The Investigator concluded that it was a stillbirth. The stillborn baby died from an acute foetal distress consecutive to amniotic fluid loss and prolapse of the umbilical cord. No congenital abnormalities were reported. After delivery, the mother had genital haemorrhage and physical asthenia. Haemoglobin was at 4 g/dL. Postpartum haemorrhage complicated by non-tolerated anaemia and got transfusion with 450 mL of whole blood. The patient resolved after treatment.

Adult female participant with intermediate-stage HAT. The pregnancy test at screening, Day 1 was negative. On the 6 month visit obstetrical observations showed pregnancy in good evaluation. During pregnancy she was treated for malaria at local health centre. On Day 264 after treatment, the patient left her village to go to site for planned delivery. During her journey, she complained of fever, cephalgia and lombo-hypogastralgia. Her husband decided to return to the village with her for first care at the nearest health centre, different from her usual one. Two hours later began the labour of delivery and in the evening of a newborn. The newborn was in a bad condition with a weight of 2.6 kg, height of 50 cm and an APGAR score of 4 at 1 minute and developed sepsis on the same day and died 2 days later. The death was not considered related to acoziborole (according to the Investigator and Sponsor). The mother developed CTCAE grade 3 Puerperal infection with fever and headache, which required hospitalization. She was treated repeatedly with paracetamol and ampicillin and recovered about a month later.

Pregnancy cases were reviewed to estimate drug exposure of fetuses based on the elimination half-life of acoziborole determined in participants with g-HAT who received the single oral therapeutic dose of 960 mg, ie, about 296 hours corresponding to 12.3 days. Therefore, considering that a drug is essentially eliminated from the body after five half-lives, which corresponds to about 62 days for acoziborole, a fetus was considered exposed to acoziborole in utero if the pregnancy start date (calculated from the first day of date of last menstrual period [LMP]) was estimated to be before or up to 62 days after acoziborole intake. This time frame is slightly different from that initially used in CSRs (within 83 days), which was based on acoziborole elimination half-life determined in healthy participants.

Using the recalculated time frame of 62 days, 4 foetuses out of 7 pregnancies reported during the study DNDi-OXA-02-HAT were considered exposed to the study drug in utero (mother Participants). In these cases, exposure to acoziborole occurred within 62 days before or after the estimated LMP. According to the Investigator and Sponsor, none of the two deaths or serious TEAEs in these cases were considered related to acoziborole. Follow-up data at 2 years of age showed that infants of

Participants were in good general condition. The infant of 1 Participant (foetus not exposed) was healthy but showed a delayed physical and motor development due to malnutrition.

Study DNDi-OXA-04-HAT

Eleven pregnancies were reported during the study of which 8 cases were reported in the acoziborole arm and 3 cases in the placebo arm. Of the 8 pregnancies in the acoziborole arm, 6 newborns were healthy according to the latest available follow-up information they developed normally. Narratives for the two other cases are presented below:

Adult female participant that had a positive pregnancy test at the 1-month follow-up visit. At the Month 4 visit, the trial participant reported having had genital bleeding associated with lumbo-hypo gastralgia approximately 1.5 months prior to the Month 4 visit, consecutive to the intake of traditional plants and other unknown medications. Pregnancy test was negative. Physical and gynaeco-obstetric examinations were normal at the Month 4 visit. The trial participant did not receive any treatment or procedure post-abortion. The event was not considered related to acoziborole by the investigator and the sponsor.

Adult female participant who had a negative pregnancy test on the day before administration of acoziborole. At the month 4 visit, she had fever and was diagnosed with malaria and an early pregnancy was also detected. She got treatment for the malaria infection and recovered but had another malaria infection next month for which she also got treatment. The 6-month pregnancy visit showed no specific concerns. On Day 273 after treatment, the participant had advanced age pregnancy with significant vulvar bleeding, sharp back pain and dilated cervix. The participant was transferred to a general hospital on the same day. Examination indicated that the participant was in labour: the foot of the foetus was felt during vaginal examination. Umbilical cord prolapse (not pulsative) and subsequent spontaneous expulsion of the foetus by normal vaginal delivery were reported. The trial participant was treated with oxytocin 5 IU IV infusion. Foetal death due to breech presentation with umbilical cord prolapse and prematurity was reported. The child was a female with a weight of 1.3 kg, height of 33 cm and head circumference of 27 cm. No foetal defects were observed.

In the acoziborole arm, the foetus was considered exposed to the study drug in utero in 5 cases, with 2 cases of pregnancy started before or on the day of the drug administration and 3 cases started within 62 days post-dose.

In the placebo arm, one pregnancy had no complications and the newborn was normal, whereas in 2 cases there were complications: one case of spontaneous abortion and one case of probably induced abortion.

Breastfeeding

No cases of exposure during breastfeeding were reported in clinical studies. Available pharmacokinetic data in rats have shown that acoziborole is excreted into breast milk.

5.4.7. Immunological events

Not applicable.

5.4.8. Safety related to drug-drug interactions and other interactions

See section ”pharmacology” for food effect, effect on other drugs on acoziborole and effects of

acoziborole on other drugs.

5.4.9. Vital signs and laboratory findings

5.4.9.1. Haematology

Participants with g-HAT, study DNDi-OXA-02-HAT

Notable shifts reported in >5% of participants from baseline to Day 11 and Month 18 in the overall Treated set are presented in Table 45. There were no notable shifts at any time points for platelets and basophils (levels remained <LLN).

Table 45. Notable shigts in hematology parameters from baseline to Day 11 and Month 18 – Study DNDi-OXA-02-HAT

Description	Day 11			Month 18		
	Normal values maintained	From <LLN to normal	From normal to <LLN	Normal values maintained	From <LLN to normal	From normal to <LLN
Hemoglobin[a], n (%)						
Male	43 (36.8%)	8 (6.8%)	17 (14.5%)	55 (47.0%)	49 (41.9%)	2 (1.7%)
Female	74 (81.3%)	1 (1.1%)	2 (2.2%)	71 (78.0%)	12 (13.2%)	1 (1.1%)
Neutrophils[b], n (%)						
All participants	167 (80.3%)	19 (9.1%)	11 (5.3%)	171 (82.2%)	21 (10.1%)	3 (1.4%)
Eosinophils[c], n (%)						
All participants	161 (77.4%)	15 (7.2%)	11 (5.3%)	140 (67.3%)	18 (8.7%)	27 (13.0%)
Monocytes[d], n (%)						
All participants	38 (18.3%)	27 (13.0%)	27 (13.0%)	29 (13.9%)	15 (7.2%)	33 (15.9%)
	Normal values maintained	**From >ULN to normal**	**From normal to >ULN**	**Normal values maintained**	**From >ULN to normal**	**From normal to >ULN**
Leukocytes[e], n (%)						
All participants	164 (78.8%)	18 (8.7%)	11 (5.3%)	163 (78.4%)	27 (13.0%)	4 (1.9%)
Lymphocytes[f], n (%)						
All participants	119 (57.2%)	33 (15.9%)	19 (9.1%)	118 (56.7%)	51 (24.5%)	17 (8.2%)

Abbreviations: **LLN**, lower limit of normal; **ULN**, upper limit of normal.
a LLN-ULN: female: 9.5 – 15.8 g/dL; male: 12.2 – 17.7 g/dL
b LLN-ULN: 25% – 66%
c LLN-ULN: 0.8% – 21.8%
d LLN-ULN: 4.5% – 13.1%
e LLN-ULN: 3.1 – 9.1 × 10*3/µL
f LLN-ULN: 23% – 59%
Source: 5.3.5.2 Study DNDi-OXA-02-HAT (Section 12.4.2.2).

The reported abnormal haematology parameter was anaemia (n=7) of which 6 of them were reported in participants with late-stage g-HAT. All events of anemia were resolved within the study period. The anemia was considered severe in 4 participants with late-stage g-HAT, and 2 participants had a medical history of ongoing anemia.

Other study participant populations

In study DNDi-OXA-04-HAT, no clinically significant changes in hematology parameters were observed in participants seropositive for g-HAT over the study period, except a slight decrease in the mean levels of hemoglobin observed in the acoziborole arm on Day 5 (in both male and female participants), which increased at Month 1 and returned to baseline level at Month 4.

TEAEs related to clinically significant abnormalities in hematology parameters were reported in 6 participants in the acoziborole group (4 events of anemia, 1 event of platelet count decrease and 1 event of leukocytosis), and none in the placebo group. None of these events were serious and considered drug-related. One event of anemia and one event of leukocytosis was grade 3 (severe TEAE).

Clinical pharmacology studies

No clinically significant hematology findings or shifts of clinical concern were reported.

5.4.9.2. Clinical Chemistry

Participants with g-HAT

Most participants maintained the normal values for the tested biochemistry parameters at all time points, except of BUN where both change from <LLN to normal (11% D11; 23% M18) and change from normal to <LNN was reported in 11% at D11 and 10% at M18. For albumin was changes from <LLN to normal reported in 15% at D11 and in 41% at M18 and less participants (4%) reported change from normal to <LLN.

Notable shifts reported in >5% participants from baseline to Day 11 and Month 18 in the overall Treated set are presented in Table 46. Most out-of-range values tended to normalize over the study period (from <LLN or >ULN to normal range). There were no notable shifts at any time points for total CO2 (bicarbonates), calcium and bilirubin.

Table 46. Notable shifts in biochemistry parameters from baselinen to Day 11 and Month 18 -Study DNDi-OXA-02-HAT

Description	Day 11			Month 18		
	Normal values maintained	From <LLN to normal	From normal to <LLN	Normal values maintained	From <LLN to normal	From normal to <LLN
Sodium, n (%)						
All participants	162 (77.9%)	29 (13.9%)	5 (2.4%)	141 (67.8%)	34 (16.3%)	3 (1.4%)
Chloride, n (%)						
All participants	164 (78.8%)	13 (6.3%)	0 (0.0%)	127 (61.1%)	11 (5.3%)	0 (0.0%)
Glucose, n (%)						
All participants	174 (83.7%)	8 (3.8%)	6 (2.9%)	147 (70.7%)	13 (6.3%)	9 (4.3%)
BUN, n (%)						
All participants	58 (27.9%)	33 (15.9%)	23 (11.1%)	50 (24.0%)	48 (23.1%)	21 (10.1%)
Creatinine, n (%)						
All participants	154 (74.0%)	14 (6.7%)	9 (4.3%)	133 (63.9%)	7 (3.4%)	10 (4.8%)
ALP, n (%)						
All participants	155 (74.5%)	10 (4.8%)	17 (8.2%)	143 (68.8%)	27 (13.0%)	1 (0.5%)
Albumin, n (%)						
All participants	26 (12.5%)	31 (14.9%)	8 (3.8%)	22 (10.6%)	85 (40.9%)	9 (4.3%)
	Normal values maintained	From >ULN to normal	From normal to >ULN	Normal values maintained	From >ULN to normal	From normal to >ULN
Potassium, n (%)						
All participants	151 (72.6%)	14 (6.7%)	21 (10.1%)	140 (67.3%)	15 (7.2%)	9 (4.3%)
Chloride, n (%)						
All participants	164 (78.8%)	16 (7.7%)	8 (3.8%)	127 (61.1%)	13 (6.3%)	22 (10.6%)
Creatinine, n (%)						
All participants	154 (74.0%)	20 (9.6%)	4 (1.9%)	133 (63.9%)	22 (10.6%)	3 (1.4%)
ALAT n (%)[a]						
All participants	181 (87.0%)	5 (2.4%)	11 (5.3%)	169 (81.3%)	7 (3.4%)	0 (0.0%)
ASAT, n (%)[a]						
All participants	176 (84.6%)	9 (4.3%)	13 (6.3%)	163 (78.4%)	10 (4.8%)	2 (1.0%)
Protein, n (%)						
All participants	102 (49.0%)	29 (13.9%)	18 (8.7%)	100 (48.1%)	71 (34.1%)	1 (0.5%)

Abbreviations: **ALP**, alkaline phosphatase; **ALAT**, alanine aminotransferase; **ASAT**, aspartate aminotransferase; **BUN**, blood urea nitrogen; **LLN**, lower limit of normal; **ULN**, upper limit of normal.
a For ALAT and ASAT, shifts were from >ULN and ≤2 × ULN to normal or from normal to >ULN and ≤2 × ULN.
Source: 5.3.5.2 Study DNDi-OXA-02-HAT (Section 12.4.2.2).

TEAEs related to biochemistry parameters were reported as follows: blood calcium decreased in two participants (both with early- or intermediate-stage g-HAT), blood creatinine increased in two participants (one in each cohort), blood potassium increased in two participants (one in each cohort), blood sodium decreased in two participants (both with late-stage g-HAT) and blood glucose increased in one participant with late-stage g-HAT. None of these events were considered serious or drug-related and all were resolving/resolved by EOS.

Other study participant populations

In study DNDi-OXA-04-HAT, a similar tendency to <LLN for BUN and albumin at baseline was noted in study -04. On D5 a decrease in ALP, ALAT and total bilirubin was noted, the parameters returned to baseline.

TEAEs related to clinically significant abnormalities in blood chemistry parameters were reported in 22/1206 participants (25 events): 15 events in 13/906 participants in the acoziborole arm, and

10 events in 9/300 participants in the placebo arm. None of these events were serious and considered drug-related by the investigator.

TEAEs related to abnormalities in blood chemistry parameters were reported for 1.4% of the participants; events had the PTs of Blood potassium increased (0.9% of the participants), Blood albumin decreased and Blood potassium decreased (each PT reported in 0.2% of the participants), and Hypoalbuminaemia, Hypocalcaemia and Hypoglycaemia (each PT reported singly, in 0.1% of the participants). In the placebo arm, TEAEs related to abnormalities in blood chemistry parameters were reported for 3.0% of the participants; events had the PTs of Blood potassium increased (in 2.0% of the participants), Blood calcium increased, Aspartate aminotransferase increased, and Blood sodium decreased (each PT reported singly, in 0.3% of the participants).

Most of these TEAEs were severe (19 events, mainly blood potassium increased), but they either recovered or were recovering by EOS.

The review of all TEAEs of Blood potassium increased reported in studies DNDi-OXA-02-HAT and DNDi-OXA-04-HAT for participants exposed to acoziborole or placebo identified confounding factors such as pre-existing increased serum potassium levels, renal impairment, dehydration and comedication with captopril. All events of increased potassium reported in study -02 and -04 are described in the Table *47*.

Table 47. Details of all TEAEs of "Blood potassium increased" reported in acoziborole trials

Participant ID	CTCAE Toxicity Grade	Time to onset (study days)[a]	Duration (study days)[a]	Comment
DNDi-OXA-04-HAT - Acoziborole				
	Grade 3	5	113	ECG normal, Renal function normal at screening, Asymptomatic, Suspected pseudohyperkalaemia
	Grade 2	5	27	Serum potassium increased at screening, Asymptomatic, Renal function normal, Suspected pseudohyperkalaemia in the context of increased serum potassium at screening
	Grade 3	5	28	BMI: 17.75 kg/m^2 at screening, Increased serum potassium at screening, Renal function normal, ECG normal, Asymptomatic, Suspected pseudohyperkalaemia in context of increased serum potassium at screening
	Grade 3	5	35	Pre-existing hypertension, abnormal baseline ECG (Left ventricular hypertrophy with ST - T segment abnormality), captopril for hypertension, Increased serum potassium at screening, Renal function normal, Suspected pseudohyperkalaemia in the context of increased serum potassium at screening and concomitant medication with captopril

Participant ID	CTCAE Toxicity Grade	Time to onset (study days)[a]	Duration (study days)[a]	Comment
	Grade 3	31	93	BMI: 16.44kg/m^2 at screening, Serum creatinine increased at screening, but normal at time of event, Serum potassium at the upper limit of normal at screening, Asymptomatic, Suspected pseudohyperkalaemia
	Grade 3	123	Unknown	Asymptomatic, TTO not supportive of causal relationship, Suspected pseudohyperkalaemia
	Grade 3	123	Unknown	Increased serum potassium at screening, Asymptomatic, Renal function normal, TTO not supportive of causal relationship, Suspected pseudohyperkalaemia in the context of increased serum potassium at screening
	Grade 3	123	Unknown	Increased serum potassium at screening, Asymptomatic, Renal function normal, TTO not supportive of causal relationship, Suspected pseudohyperkalaemia in the context of increased serum potassium at screening
DNDi-OXA-04-HAT- Placebo				
	Grade 3	4	4	Renal function normal at screening, Asymptomatic, ECG reported as abnormal but not clinically significant, Suspected pseudohyperkalaemia
	Grade 2	5	27	Increased serum potassium at screening, ECG normal, Renal function normal, Asymptomatic, Suspected pseudohyperkalaemia in the context of pre-existing increased serum potassium levels
	Grade 3	121	Unknown	Increased serum potassium at screening, Serum creatinine mildly elevated, Urea normal, Asymptomatic, Suspected pseudohyperkalaemia in the context of pre-existing increased serum potassium levels
	Grade 2	32	85	Increased serum potassium at screening, Renal function normal, Asymptomatic, Suspected pseudohyperkalaemia in the context of increased serum potassium at screening
	Grade 2	41	84	Increased serum potassium at screening, Renal function normal, Asymptomatic, Suspected pseudohyperkaelaemia in the context of increased serum potassium at screening
	Grade 3	53	78	BMI: 18.18 kg/m^2 at screening, Renal function normal, Asymptomatic, Suspected pseudohyperkalaemia

Participant ID	CTCAE Toxicity Grade	Time to onset (study days)[a]	Duration (study days)[a]	Comment
	Grade 2	124	Unknown	Renal function normal, Asymptomatic, Suspected pseudohyperkalaemia
DNDi-OXA-02-HAT - Acoziborole				
	Grade 4	11	3	Renal impairment and increased serum potassium at screening, Concurrent dehydration, fever and renal impairment
	Grade 2	103	87	Serum potassium increased on D5 (5.4 mmol/L) and D11 (5.2 mmol/L) Participant asymptomatic, TTO and duration not supportive of causal relationship, Suspected pseudohyperkalaemia

Sources: DNDi-OXA-02-HAT CSR, Listings 16.2.5.1, 16.2.5.5, 16.2.8.1.1 and 16.2.9, and DNDi-OXA-04-HAT CSR, Listings 16.2.4.2, 16.2.4.4, 16.2.7.1 and 16.2.8.2

Abbreviations: BMI, body mass index; **CTCAE,** Common Terminology Criteria for Adverse Events; **D**, day; **ECG**, electrocardiogram; **ID,** identifier; **TTO**, time to onset

a Time to onset and duration are modified by the timing of study assessments and are provided by study day. The study day of acoziborole administration was Day 1.

Clinical pharmacology studies

In study DNDiOXA001, mean values of biochemistry parameters remained within normal bounds throughout the study duration, except in Part VI for ASAT and ALAT which showed increased levels considered as non-clinically significant. No trends of abnormalities under exposure of acoziborole were detected in the following parameters: bilirubin, pancreatic function (glycemia, lipase and amylase), lipid profile (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol), and renal function (creatinine, urea, ions).

The most frequent abnormalities were high CPK, high LDL, low LDL and HDL, and low urea. Most of them were previously reported before treatment initiation and considered as not clinically significant.

Elevated ASAT and ALAT values >3 X ULN led to the report of TEAEs in 2 participants with placebo. With acoziborole, 6 participants had elevated ASAT values associated with TEAEs, and 7 participants had elevated ALAT values associated with TEAEs. Elevated ALP values were reported in parallel with abnormal ASAT and ALAT values in 1 participant with acoziborole, and abnormal GGT values were reported in parallel with abnormal ASAT and ALAT values in the 2 participants with placebo, and 3 participants with acoziborole. Moreover, elevated levels of CPK >3 X ULN were observed in 52/110 (47.3%) participants in Part I (40 with acoziborole and 12 with placebo), and a TEAE was reported in 6 cases (one placebo, and five acoziborole). As most participants had already elevated CPK before treatment initiation, and abnormalities were reported in both the placebo and acoziborole (different dose levels) cohorts, it seemed unlikely that CPK elevation could be related to acoziborole. Most of these abnormal values returned to normal by the EOS, except for the 6 participants with high levels of CPK that were still above ULN at EOS.

The proportion of participants presenting any abnormalities was comparable in all study groups including placebo, and appeared independent from time, drug administration or dose of acoziborole. None of the participants met Hy's law criteria for drug-induced liver injury, and few abnormalities were observed at the therapeutic dose of 960 mg.

In study DNDi-OXA-03-HAT, most mean values for clinical chemistry parameters were within the normal ranges at baseline (Day 1, pre-dose) and each post-dose time point. Increased blood glucose was reported in one participant on D119 and increased CPK was reported in one participant on D15 (related to exercise).

In study DNDi-OXA-07-HAT, mean values of biochemistry parameters remained within normal bounds during the study, and no significant change or trend was observed. One event of elevated ALAT was reported on D21 (9 days after administration of midazolam).

5.4.9.3. Thyroid Function

Participants with g-HAT

Notable shifts reported in >5% of participants from baseline to Day 11 and Month 18 are summarized in Table 48. A change from baseline in TSH (8%), T3 (5%) and T4 (10%) was noted on D11. No TEAEs related to thyroid function parameters were reported during this study.

Table 48. Notable shigts in thyroid function parameters from baseline to Day 11 and month 18 -Study DNDi-OXA-02-HAT

Description	Day 11			Month 18		
	Normal values maintained	From <LLN to normal	From normal to <LLN	Normal values maintained	From <LLN to normal	From normal to <LLN
Free tri-iodothyronine, n (%)						
All participants	72 (34.6%)	65 (31.3%)	10 (4.8%)	64 (30.8%)	68 (32.7%)	12 (5.8%)
Free thyroxine, n (%)						
All participants	127 (61.1%)	13 (6.3%)	20 (9.6%)	127 (61.1%)	22 (10.6%)	22 (10.6%)
	Normal values maintained	**From >ULN to normal**	**From normal to >ULN**	**Normal values maintained**	**From >ULN to normal**	**From normal to >ULN**
Free thyroxine, n (%)						
All participants	127 (61.1%)	14 (6.7%)	4 (1.9%)	127 (61.1%)	13 (6.3%)	4 (1.9%)
TSH[a], n (%)						
All participants	173 (83.2%)	1 (0.5%)	16 (7.7%)	185 (88.9%)	6 (2.9%)	3 (1.4%)

Abbreviations: **LLN**, lower limit of normal; **TSH**, thyroid stimulating hormone; **ULN**, upper limit of normal.

Note: normal ranges were 4.0-8.3 pmol/L for free tri-iodothyronine, 10.6-19.4 pmol/L for free thyroxine, and 0.25-5 µIU/mL for TSH.

a. No values were >2 X ULN

Following acoziborole administration,6 participants with g-HAT (pivotal study, DNDi-OXA-02-HAT) had a low TSH. All these participants reported a TSH value of 0.05 mIU/L (reference range 0.25 to 5.0 mIU/L). Four were associated with normal fT3 and fT4 values, and 2 had a low fT4 result, which is not consistent with a diagnosis of hyperthyroidism. The low TSH test results resolved spontaneously at the next follow-up visit, and none were reported as clinically significant.

Table 49. Illustrating the summary of time to onset of low thyrotropin (TSH) and associated thyroid function test results (DNDi-OXA-02-HAT)

DNDi-OXA-02-HAT Participant ID, Sex	**Study day**	**Thyroid hormone levels (reference range)**		
		TSH (mIU/L) [0.25 – 5.0]	fT3 (pmol/L) [4.0 – 8.3]	fT4 (pmol/L) [10.6 – 19.4]
	Baseline	2.67	3.2 (low)	14.48
	D 11	1.96	3.26 (low)	12.02
	D 97	0.05 (low)	4.99	14.97
	D 183	1.28	4.62	10.76
	Baseline	2.41	4.42	13.3
	D 91	0.05 (low)	6.95	15.69
	D 183	0.87	4.19	14.18
	Baseline	0.91	2.97	11.24
	D 11	1.73	5.24	9.1 (low)
	D 91	0.05 (low)	4.33	6.47 (low)
	D 183	0.59	4.31	10.65
	Baseline	3.05	3.04	14.47

DNDi-OXA-02-HAT Participant ID, Sex	Study day	Thyroid hormone levels (reference range)		
		TSH (mIU/L) [0.25 – 5.0]	fT3 (pmol/L) [4.0 – 8.3]	fT4 (pmol/L) [10.6 – 19.4]
	D 365	1.92	3.59 (low)	12.27
	D 550	0.05 (low)	4.1	13.97
	Baseline	1.1	4.83	13.62
	D 11	0.17 (low)	4.37	9.0 (low)
	D 88	0.38	4.07	11.06
	Baseline	0.69	3.38	18.34
	D 11	2.18	5.36	15.74
	D 92	0.05 (low)	3.4	12.4
	D 199	1.12	4.31	13.47

Source: DNDi-OXA-02-HAT CSR Listing 16.2.9 Individual Data Listings - Laboratory Values

Abbreviations: **F,** female participant; **fT3**, free triiodothyronine; **fT4**, free thyroxine; **ID**, identifier; **TSH,** thyroid-stimulating hormone

Other study participant populations

Thyroid function was not investigated in study DNDi-OXA-04-HAT.

Clinical pharmacology studies

In study DNDiOXA001 Part I and Part VI, the following abnormal values and clinically significant variations were reported for free tri-iodothyronine, free thyroxin, and TSH:

- Free tri-iodothyronine values slightly above the ULN of 6.8 pM were reported with acoziborole, as well as with placebo (values ranging from 6.9 to 11.8 pM). All the increases were transient and relatively limited. One isolated measurement was clinically significant in 3/128 (2.3%) participants (2 participants with 160 mg acoziborole, and 1 participant with 240 mg acoziborole).
- Free thyroxin values slightly below the LLN of 12 pM were observed in some participants in almost all dose level groups and the placebo group (values ranging from 9.2 to 11.9 pM). Moreover, 3/128 (2.3%) participants (2 with placebo and 1 with 240 mg acoziborole) had sporadic free thyroxin levels slightly above the ULN of 22 pM. All these abnormalities were considered not clinically significant except in 1 participant.
- TSH level was above the ULN of 4.2 mIU/L in at least 1 participant in almost all dose level groups (except doses of 20 mg and 120 mg) and in the placebo group. All elevations were limited and not clinically significant. In 2 Participants (D64), decreases in TSH values below the LLN of 0.27 mIU/L were observed at the same time as clinically significantly elevated free tri-iodothyronine values.

There was no trend suggesting a dose effect on these 3 parameters. It cannot be concluded that acoziborole exposure impacted on the thyroid function. The change in thyroid hormones in 2 participants were reported as TEAEs.

In study DNDi-OXA-03-HAT, an increase in mean TSH was observed on one occasion, which could be attributed to physiological variation within the normal range values, and no thyroid-related symptoms were observed in any participants. One participant had marginal non-clinically significant elevations in free tri-iodothyronine and free thyroxine levels at 2 time points (88 days and 118 days post-dose, respectively).

In study DNDiOXA001 did 3 participants report abnormal thyroid function tests (1 Participants [160 mg], 1 participant [160 mg], and 1 participant [240 mg]). The study was conducted in healthy participants in the south of France (region of Grenoble) and were reported as related by the investigator. All 3 participants were asymptomatic. One of these cases was considered serious. All 3 reported TEAEs were of mild intensity and had resolved spontaneously by the last follow-up visit. Narratives are presented below:

Participant (acoziborole 240 mg)

A serious adverse event of "Asymptomatic Hyperthyroidism" was reported for an adult participant with a body mass index of 27.6 kg/m2 The participant received a single dose of 240 mg acoziborole on 27 September 2013. Thyroid function was normal at baseline. On 03 December 2013, 67 days after acoziborole administration, the TSH of this participant was low (0.076 mIU/L; reference range 0.27 to 42.0 mIU/L) and with normal fT3 (5.7 pmol/L; reference range 3.1 to 6.8 pmol/L) and fT4 (18.4 pmol/L; reference range 12 to 22 pmol/L). Per protocol, administration of activated charcoal (Toxicarbone®) had started on 01 October 2013 and was ongoing at the time of the event (last dose 31 December 2013). The Investigator considered the abnormal thyroid function test results as clinically significant and possibly related to acoziborole. The participant did not develop any clinical signs of hyperthyroidism and no other TEAEs were reported for this participant.

The thyroid function spontaneously returned to normal within 6 weeks (13 January 2014: TSH 0.709 mIU/L, fT3 4.1 pmol/L and fT4 11.7 pmol/L; confirmed on 27 January 2014). An echography on 23 December 2013 reported a goitre of the right thyroid lobe and a cyst (without abnormality). A T99m scintigraphy on 03 January 2014 described diffuse hypofixation. Anti-thyroglobulin antibodies were normal at baseline (tested on a stored sample) and increased on 15 and 31 December 2013 and 13 January 2014 (171 IU/L, 131 IU/L, and 151 IU/L, respectively; reference range below 115 IU/L). Anti-thyroid peroxidase and anti-thyrotropin receptor antibodies were normal at baseline until the last testing on 13 January 2014.

Participant (acoziborole 160 mg)

A non-serious TEAE of Thyroid Function Test Abnormal was reported for an adult participant following an administration of 160 mg of acoziborole on 16 May 2013. Thyroid function was normal at baseline. On 22 July 2013, 68 days after administration of acoziborole, a low TSH (0.071 mIU/L), an increased fT3 (9.8 pmol/L), and a normal fT4 (19.7 pmol/L) were reported. On 26 July 2013, the TSH was still low (0.115 mIU/L) with normal fT3 (5.6 pmol/L) and fT4 (12.2 pmol/L). By 19 August 2013, TSH, fT3, and fT4 returned spontaneously to normal levels. The TSH remained normal on 13 November 2013. The Investigator considered the abnormal thyroid function tests as clinically significant and related to acoziborole. No other TEAEs were reported for this participant.

Participant (acoziborole 160 mg)

A non-serious TEAE of Thyroid Function Test Abnormal was reported for an adulte participant following an administration of acoziborole 160 mg on 16 May 2013. Thyroid function was normal at baseline. On

22 July 2013, 53 days after administration of acoziborole, an increased fT3 (7.2 pmol/L) was reported with a normal TSH (2.3 mIU/L) and normal fT4 (16.1 pmol/L) and considered clinically significant. Previous recordings of increased TSH or fT3 were not considered clinically significant. This participant had also reported TEAEs of aphthous stomatitis, diarrhoea, myalgia, and nausea, which were all considered not related to acoziborole. All these TEAEs resolved spontaneously and were of mild to moderate severity.

5.4.9.4. Adrenal hormones and testosterone

Based on preclinical observations in the 13-week toxicity studies in the rat and dog (see pre-clinical part), the potential effect of acoziborole on plasma/serum levels of selected hormones (adrenocorticotropic hormone [ACTH], aldosterone, androstenedione, cortisol, dehydroepiandrosterone sulfate [DHEAS] and testosterone) was evaluated in participants who received the 960 mg single oral dose of acoziborole in Period 2 of study DNDi-OXA-07-HAT (N = 19).

No data on ACTH, cortisol, aldosterone, androstenedione and testosterone have been evaluated in the two clinical studies. The only available data in humans on those parameters are from 19 participants in study DNDi-OXA-07-HAT who received a single dose of 960 mg acoziborole.

In study -07, blood samples were collected for determination of plasma/serum concentration of selected hormones (serum cortisol, plasma ACTH, serum aldosterone, serum DHEA-S, serum androstenedione and serum testosterone) at the following times: pre-dose as baseline (i.e. on Day 2, Day 3 and Day 4) then on Day 12 (pre-dose), Day 14 and Day 21, post-dose acoziborole. All blood samples for hormones were taken in the morning (between 07:02 and 09:01 a.m.) before breakfast. For each hormone, values obtained at pre-dose (i.e. on Day 2, Day 3 and Day 4) were pooled and mean value was used as baseline to decrease the variability. The study population included only male participants between 18 to 55 years of age.

The mean plasma level of ACTH (produced by the anterior pituitary gland) increased 2 times 48 hours post acoziborole dosing (ie, Day 14) compared to baseline (with high variability between participants). The mean serum level of cortisol, aldosterone and androstenedione also increased 48 hours post acoziborole dosing (+36%, +20%, and +35%, respectively), whereas the level of DHEAS decreased by 18% 48 hours post-dosing. No participant had low levels of cortisol following acoziborole administration. No participant had an increased level of ACTH in association with a low level of cortisol that could suggest adrenal insufficiency. Testosterone serum levels were not changed or changed up to +10% following acoziborole dosing.

Table 50. Selected hormones – Descriptive statictics of observed valued and changes from baseline

			Raw data			Change from baseline			
Selected hormones	**Period**	**Day**	**N**	**Mean (SD)**	**Min/Median/Max**	**N**	**Mean (SD)**	**95% CI**	**Min/Median/Max**
Plasma ACTH (pg/mL)	Period 1	Baseline	19	38.88 (17.45)	14.4/33.90/83.6				
	Period 2	Day 12	19	28.82 (10.53)	11.6/26.80/51.1	19	-9.89 (14.38)	-16.83 ; -2.96	-44.0/-9.00/17.0
		Day 14	19	80.04 (70.89)	25.8/51.20/257.0	19	41.26 (75.91)	4.67 ; 77.85	-55.0/21.00/236.0
		Day 21	19	49.60 (55.94)	12.3/36.40/272.0	19	10.68 (55.82)	-16.22 ; 37.59	-54.0/3.00/219.0
Serum DHEA-S (nmol/L)	Period 1	Baseline	19	7.70 (1.63)	4.4/7.84/10.9				
	Period 2	Day 12	19	8.24 (1.54)	5.1/8.35/10.7	19	0.47 (0.51)	0.23 ; 0.72	0.0/0.00/1.0
		Day 14	19	6.38 (1.72)	3.4/6.23/9.6	19	-1.26 (1.33)	-1.90 ; -0.62	-4.0/-1.00/1.0
		Day 21	19	4.49 (1.01)	2.6/4.57/5.9	19	-3.16 (1.46)	-3.86 ; -2.45	-6.0/-3.00/-1.0
Serum aldosterone (nmol/L)	Period 1	Baseline	19	304.37 (69.77)	213.0/293.33/455.7				
	Period 2	Day 12	19	250.79 (102.22)	146.0/217.00/508.0	19	-53.58 (98.09)	-100.86 ; -6.30	-186.0/-54.00/215.0
		Day 14	19	371.16 (110.47)	220.0/363.00/692.0	19	66.79 (111.28)	13.15 ; 120.42	-145.0/75.00/335.0
		Day 21	19	408.00 (122.68)	202.0/396.00/794.0	19	103.63 (122.37)	44.65 ; 162.61	-63.0/81.00/437.0
Serum androstenedione (nmol/L)	Period 1	Baseline	19	71.09 (11.99)	51.0/74.33/94.3				
	Period 2	Day 12	19	69.63 (16.57)	44.0/69.00/97.0	19	-1.42 (16.11)	-9.19 ; 6.34	-29.0/3.00/31.0
		Day 14	19	96.21 (24.66)	57.0/97.00/151.0	19	25.16 (20.87)	15.10 ; 35.22	-12.0/27.00/64.0
		Day 21	19	95.89 (25.88)	53.0/91.00/148.0	19	24.84 (24.38)	13.09 ; 36.59	-24.0/27.00/80.0
Serum cortisol (nmol/L)	Period 1	Baseline	19	328.63 (84.88)	187.7/325.00/523.7				
	Period 2	Day 12	19	378.79 (54.02)	272.0/372.00/479.0	19	50.11 (72.66)	15.08 ; 85.13	-128.0/57.00/147.0
		Day 14	19	446.00 (103.24)	213.0/481.00/572.0	19	117.32 (135.30)	52.10 ; 182.53	-167.0/93.00/309.0
		Day 21	19	432.37 (110.85)	179.0/420.00/569.0	19	103.68 (125.49)	43.20 ; 164.17	-190.0/114.00/285.0
Serum testosterone (nmol/L)	Period 1	Baseline	19	18.11 (5.77)	11.2/17.33/29.8				
	Period 2	Day 12	19	19.91 (5.58)	11.2/18.30/32.1	19	1.68 (3.25)	0.12 ; 3.25	-8.0/2.00/8.0
		Day 14	19	20.04 (6.42)	9.3/18.30/30.6	19	1.95 (3.39)	0.31 ; 3.58	-5.0/2.00/7.0
		Day 21	19	21.44 (7.63)	9.8/20.10/40.3	19	3.32 (3.96)	1.41 ; 5.22	-3.0/3.00/16.0

The reference values are presented in the Table 51.

Table 51. Reference values for hormones (for male adults) - Study DNDi-OXA-07-HAT

Hormone	Age group (years)	Reference values (males)
DHEA-S	> 14 to 19	1.91 to 13.4 µmol/L
	> 19 to 24	5.73 to 13.4 µmol/L
	> 24 to 34	4.34 to 12.2 µmol/L
	> 34 to 44	2.41 to 11.6 µmol/L
	> 44 to 54	1.2 to 8.98 µmol/L
	> 54 to 64	1.4 to 8.01 µmol/L
Testosterone (Total)	0 to 50	8.60 to 29.00 nmol/L
	51 and older	6.60 to 25.70 nmol/L
Cortisol (a.m.)	All ages	133 to 537 nmol/L
ACTH	All ages	7.2 to 63.3 pg/mL
Androstenedione	18 to 30	50 to 220 ng/dL
	31 to 50	40 to 190 ng/dL
	51 to 60	50 to 220 ng/dL
Aldosterone (supine)	All ages	103 to 859 pmol/L

Abbreviations: ACTH, Adrenocorticotropic hormone; **a.m.,** ante meridian; **DHEA-S,** Dehydroepiandrosterone sulfate

5.4.9.5. Urinalysis

No urinalysis was performed in studies DNDi-OXA-02-HAT and DNDi-OXA-04-HAT.

No clinically significant urinalysis findings were recorded in study DNDiOXA001.

In study DNDi-OXA-07-HAT, 3/20 healthy participants reported at least a positive result for urinalysis between the first drug administration on Day 1 and EOS: 1 participant had a positive result for protein on Day 11 (pre-dose), 1 participant had a positive result for occult blood on Day 22 (post-dose), and 1 participant had positive results for bilirubin, ketone, occult blood, protein and urobilinogen at EOS. No rechecks were performed. Furthermore, 2/20 participants had low urine density values. These abnormal findings were considered as non-clinically significant and no TEAEs were reported.

5.4.9.6. Blood Pressure and Orthostatic Changes

Participants with g-HAT

In study DNDi-OXA-02-HAT, mean values for systolic BP, diastolic BP, HR and RR remained relatively stable from baseline to Month 18. TEAEs of hypertension were reported in 2/208 (0.96%) participants overall (1 participant in each disease-stage cohort), and TEAEs of hypotension and orthostatic hypotension were each reported in 1/208 (0.5%) participant (both participants with late-stage g HAT). None of these events were serious and considered as drug-related; all were of mild or moderate severity and resolved by EOS.

Karnofsky performance status, general health status and body weight generally improved during the study.

Other study participant populations

In study DNDi-OXA-04-HAT, no significant changes in BP or orthostatic parameters were observed in participants seropositive for g-HAT and the general status of the participants (BMI, and Karnofsky performance score) was stable over time.

TEAEs of hypertension, BP increased, BP decreased, tachycardia, and pyrexia were reported in less than 1% of participants overall and in each arm. None of these events were serious. In total, 4 events of hypertension were severe (3 in the acoziborole arm and 1 in the placebo arm). The 3 severe events of hypertension in the acoziborole arm were as follows:

- Elderly participant was diagnosed with hypertension grade 3 on D32. The event was not resolved at the end of study.
- Elderly participant was diagnosed with hypertension grade 3 on D39. The event resolved, but the duration of the event has not been described.
- Elderly participant that was diagnosed with hypertension grade 3 on D33. The event resolved after 20 days.

Three events were assessed as drug-related (2 events of pyrexia in the acoziborole arm on Day 1 which was resolved on the same day, and 1 event of tachycardia in the placebo arm).

Clinical pharmacology studies

Overall, no clinically significant abnormalities in blood pressure or orthostatic parameters were considered as related to acoziborole in healthy participants included in the pharmacology studies.

5.4.9.7. Electrocardiogram

5.4.9.7.1. Participants with g-HAT, study DNDi-OXA-02-HAT

Electrocardiogram findings in the Treated set of study DNDi-OXA-02-HAT (N = 208) are summarized below.

Effects of acoziborole on heart rate

The mean (±SD) HR at baseline was 67.6±12.5, 70.8±11.3 and 69.4±12.6 bpm in participants with early-, intermediate- and late-stage g-HAT, respectively. The central tendency analysis indicated that the single-dose administration of acoziborole caused a transient increase in HR which was maximal 9 hours post-dose (ΔHR of 13.3 bpm) but had dissipated 24 hours later (Figure 24).

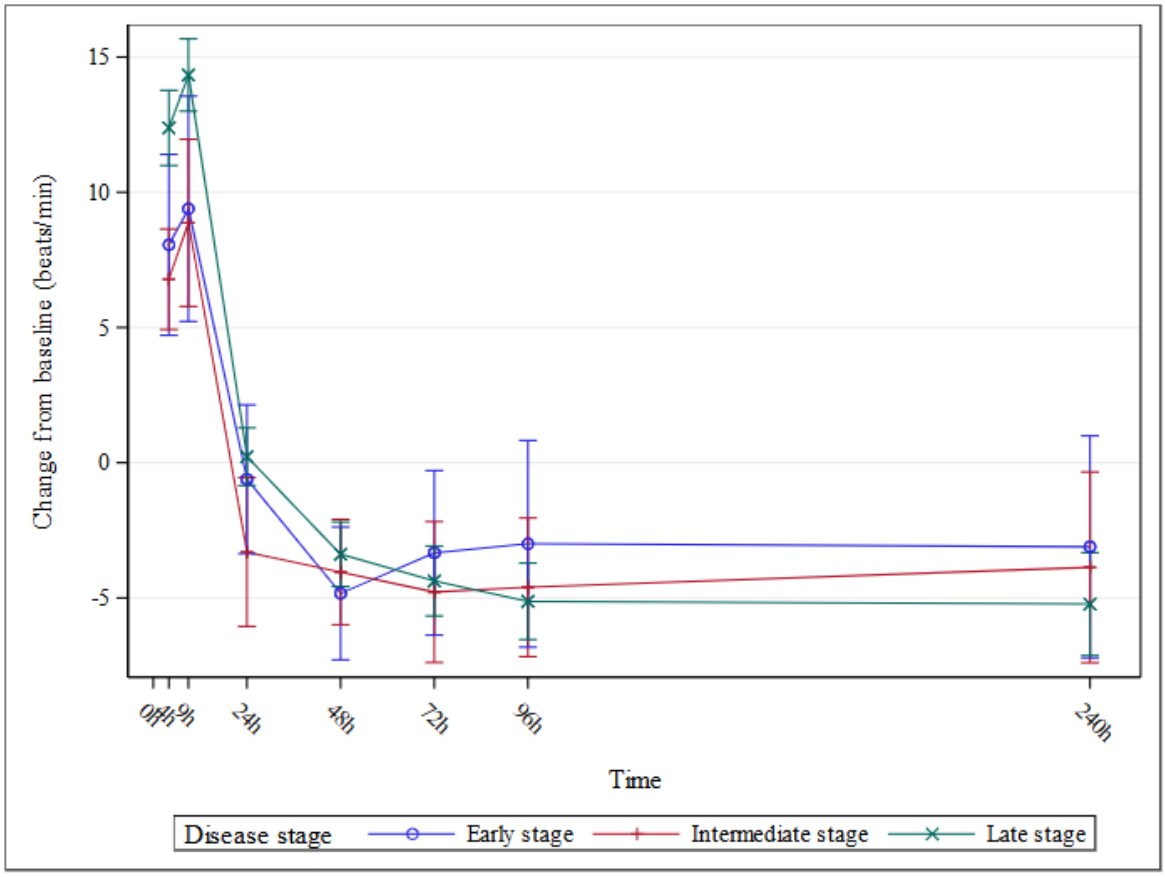


Figure 23. Analysis of central tendency of ECD mean heart rate (beats/min) – Mean changes from baseline and 95% CI

The categorical analysis also showed that a high proportion of participants (87/208 [41.8%]) had a relative ΔHR >25%. The graphical C-R analysis indicated that this transient tachycardic effect was not related to acoziborole blood concentration (see section 2), as when concentrations were low, HR increased, and when concentrations increased there was no increase but rather a small decrease in HR.

Effect of acoziborole on QTcF

Descriptive statistics for the absolute values and for the changes from baseline for QTcF are provided in Table 52 and presented graphically in Figure 25 for the change from baseline.

Baseline mean (±SD) values of QTcF were 402.0±17.1, 406.9±19.0 and 396.3±21.2 ms in participants with early-, intermediate - and late-stage g-HAT, respectively. The decrease in QTcF was

observed in each disease-stage group of participants, and was more pronounced in the participants with early-stage g-HAT, with a largest mean ΔQTcF of -18.1 ms at 96 hours (Day 5), ie, at the plateau of acoziborole plasma concentrations versus -11.6 ±9.8 ms on Day 4 in participants with intermediate-stage g-HAT and -11.9±12.0 ms at 9 hours post dose in participants with late-stage g-HAT. The mean ΔQTcF at 96 hours was -11.0 ms (95% CI: [-12.4, -9.6] ms) in the overall participant population. During the 240-hour observation period, the mean QTcF did not return to baseline values, which could be related to the long elimination half-life of acoziborole (of around 296 hours, ie, 12.3 days).

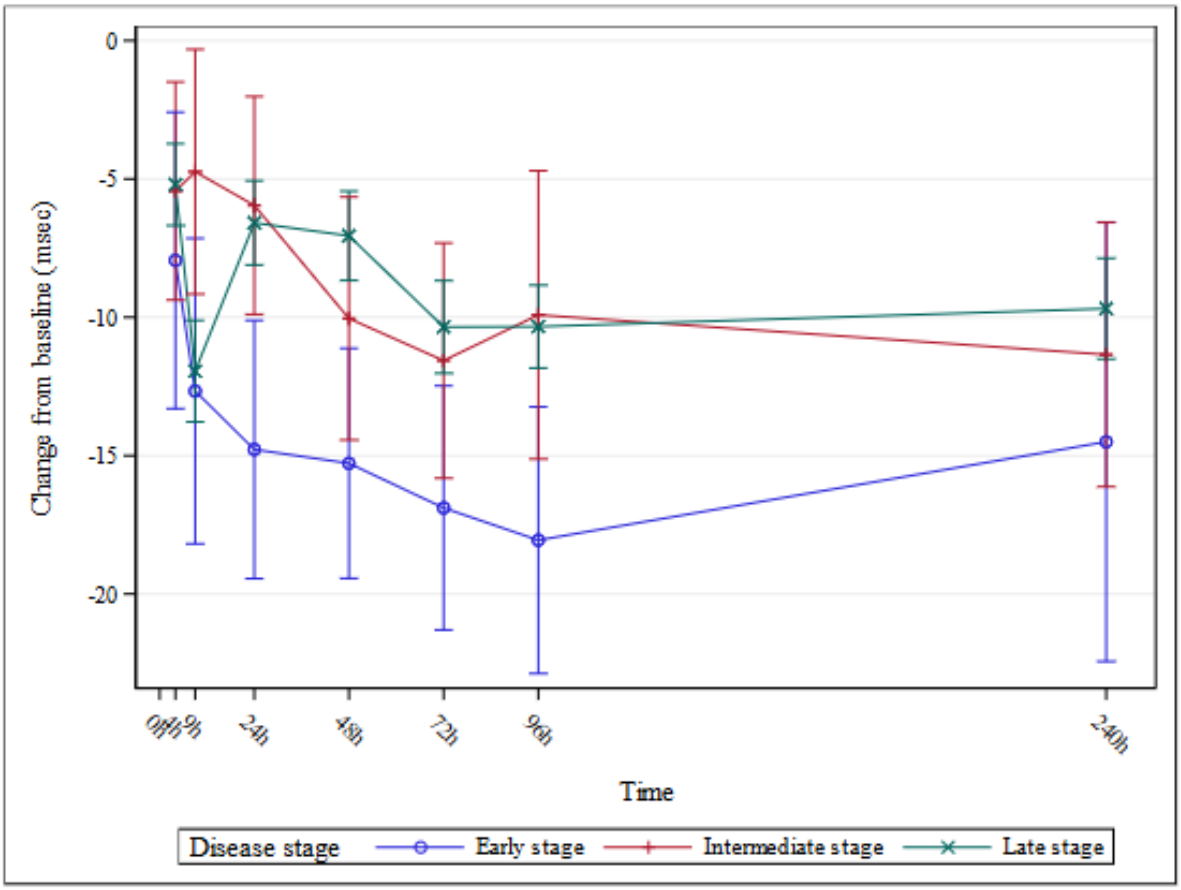


Figure 24. Analysis of central tendency of QT cF interval, aggretate (msec) – Mean changes from baseline and 95% CI

Table 52. Analysis of central tendency of QTcF internaval, aggregate (msec) – Descriptive statistics on original values and change from baseline

			Raw data			Change from baseline (Δ)			
Hat Stage	Study Day	Time Point	N	Mean (SD)	Min/Median/Max	N	Mean (SD)	95% CI	Min/Median/Max
Early stage	Day 1	Pre-dose	18	402.0 (17.1)	360/405.0/425				
		4 h	18	394.1 (18.5)	343/394.0/423	18	-7.9 (10.8)	(-13.3; -2.6)	-32/-8.5/15
		9 h	18	389.3 (19.4)	343/389.5/419	18	-12.7 (11.1)	(-18.2; -7.1)	-32/-12.0/4
		24 h	18	387.2 (18.3)	356/391.0/417	18	-14.8 (9.4)	(-19.4; -10.1)	-34/-13.0/-3
		48 h	18	386.7 (18.0)	353/390.5/415	18	-15.3 (8.4)	(-19.4; -11.1)	-31/-13.5/-2
		72 h	18	385.1 (18.6)	347/392.0/406	18	-16.9 (8.9)	(-21.3; -12.5)	-35/-18.0/-3
		96 h	18	383.9 (16.7)	349/384.5/408	18	-18.1 (9.7)	(-22.9; -13.2)	-33/-21.5/2
		240 h	18	387.5 (17.3)	352/391.5/410	18	-14.5 (16.0)	(-22.4; -6.6)	-47/-13.5/29
Intermediate stage	Day 1	Pre-dose	23	406.9 (19.0)	379/410.0/453				
		4 h	23	401.5 (15.9)	373/402.0/426	23	-5.4 (9.1)	(-9.4; -1.5)	-28/-6.0/10
		9 h	23	402.2 (16.0)	373/404.0/427	23	-4.7 (10.2)	(-9.2; -0.3)	-31/-3.0/20
		24 h	23	401.0 (20.2)	370/403.0/432	23	-6.0 (9.1)	(-9.9; -2.0)	-23/-5.0/15
		48 h	23	396.9 (19.0)	369/398.0/429	23	-10.0 (10.2)	(-14.4; -5.7)	-31/-9.0/15
		72 h	23	395.3 (18.6)	361/400.0/428	23	-11.6 (9.8)	(-15.8; -7.3)	-32/-10.0/16
		96 h	23	397.0 (18.6)	365/398.0/427	23	-9.9 (12.0)	(-15.1; -4.7)	-37/-12.0/16
		240 h	23	395.6 (21.2)	354/400.0/435	23	-11.3 (11.0)	(-16.1; -6.6)	-39/-12.0/20
Late stage	Day 1	Pre-dose	167	396.3 (21.2)	347/395.0/483				
		4 h	166	391.0 (21.1)	336/392.0/477	166	-5.2 (9.6)	(-6.7; -3.7)	-40/-3.5/21
		9 h	167	384.3 (21.4)	326/386.0/463	167	-11.9 (12.0)	(-13.8; -10.1)	-56/-9.0/18
		24 h	167	389.7 (22.3)	329/390.0/479	167	-6.6 (10.0)	(-8.1; -5.1)	-33/-6.0/26
		48 h	166	389.1 (22.0)	333/390.0/481	166	-7.1 (10.5)	(-8.7; -5.4)	-39/-8.0/37
		72 h	166	385.8 (20.6)	332/386.0/456	166	-10.3 (10.9)	(-12.0; -8.7)	-54/-10.0/21
		96 h	166	385.8 (21.6)	332/387.0/479	166	-10.3 (9.8)	(-11.8; -8.8)	-41/-10.0/23
Late stage	Day 1	240 h	166	386.5 (21.8)	327/387.5/457	166	-9.7 (11.9)	(-11.5; -7.9)	-41/-10.0/47
All	Day 1	Pre-dose	208	397.9 (20.8)	347/398.5/483				
		4 h	207	392.4 (20.6)	336/393.0/477	207	-5.5 (9.7)	(-6.8; -4.1)	-40/-4.0/21
		9 h	208	386.7 (21.4)	326/388.0/463	208	-11.2 (11.9)	(-12.8; -9.6)	-56/-9.0/20
		24 h	208	390.7 (22.0)	329/391.5/479	208	-7.2 (10.1)	(-8.6; -5.9)	-34/-7.0/26
		48 h	207	389.8 (21.4)	333/391.0/481	207	-8.1 (10.6)	(-9.5; -6.7)	-39/-8.0/37
		72 h	207	386.8 (20.3)	332/386.0/456	207	-11.1 (10.8)	(-12.5; -9.6)	-54/-10.0/21
		96 h	207	386.9 (21.1)	332/387.0/479	207	-11.0 (10.2)	(-12.4; -9.6)	-41/-11.0/23
		240 h	207	387.6 (21.5)	327/389.0/457	207	-10.3 (12.2)	(-12.0; -8.6)	-47/-11.0/47

Source Appendix 16.2.8 Listing of Individual Laboratory Measurements by Patient

The categorical analysis showed that no participant had a post-baseline QTcF value <320 ms or >500 ms, or a ΔQTcF >60 ms. It is noted that 36/208 (17.3%) participants had a post-baseline QTcF value <360 ms at any time point, indicating shortening of the QT interval. Of them, 5 participants already had a baseline QTcF <360 ms, and 8 had a baseline QTcF between 360 and 369 ms (Table 53). The lowest post-baseline value was 326 ms.

Table 53. Categorical analysis according to threshold values for QTcF changes in participants with g-HAT (Treated set) - Study DNDi-OXA-02-HAT

	Baseline QTcF				
QTcF on acoziborole treatment, n (%)	**<340 ms**	**340 to 359 ms**	**360 to 369 ms**	**≥370 ms**	**Total**
QTcF ≥360 ms	0 (0.0%)	0 (0.0%)	1 (0.5%)	171 (82.2%)	172 (82.7%)
340 to 359 ms	0 (0.0%)	0 (0.0%)	7 (3.4%)	23 (11.1%)	30 (14.4%)
320 to 339 ms	0 (0.0%)	5 (2.4%)	1 (0.5%)	0 (0.0%)	6 (2.9%)
300 to 319 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<300 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	0 (0.0%)	5 (2.4%)	9 (4.3%)	194 (93.3%)	208 (100.0%)

Abbreviations: g-HAT, human African trypanosomiasis due to *Trypanosomia brucei gambiense*; **QTcF**, QT interval corrected according to Fridericia's formula.
Source: 5.3.5.3 Safety Data Assessment Report (SDAR).

An ECG C-R analysis was performed using ΔQTcF values (ms) and matching blood concentrations of acoziborole available in 202 participants (6 participants had non-reportable values) (see section 2). In line with the central tendency analysis, the model predicted a ΔQTcF of -9.3 ms (90% CI: [-10.1, -8.4] ms) at the observed geometric mean blood C_{max} of 10.5 µg/mL.

The review of the TEAEs showed no report of cardiac TEAEs which may be associated with shortening of the QT interval (ie, PTs of syncope, palpitation, arrhythmia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation or cardiac arrest) in any participants exposed to acoziborole in this study. The 2 participants who reported a TEAE of syncope on the same day as dosing and arrhythmia were reported on day 92 in another participant. (Table 54, the table also includes cases from study 001).

Table 54. Participants with cardiac TEAEs possibly associated with QTc decrease in clinical trials

Study ID Participant ID g-HAT stage/sex	TEAE (PT)	Time to onset	Seriousness/ Severity	Outcome	Causality assessment	Comments
DNDi-OXA-02-HAT [redacted] Late stage [redacted]	Syncope	D1 of dosing	Not serious Moderate	Resolved on the same day	Not related to acoziborole	Received 960 mg acoziborole on 10 April 2018 ~~Ongoing Wolff-Parkinson-White syndrome detected on ECG at~~ Day -4. Other TEAEs: fever & headache (both on Day 1) QTcF (ms): Pre-dose: 452; H4: 450; H9: 437; D2: 449; D3: 444; D 4: 449; D5: 449; D11: 457 Ca2+ level (mg/dL): At screening: 9.6, D5: 9.6 and D11: 10.5 K+ level (mmol/L): At screening: 5.1, D5: 4.5, D11: 6.1, M3: 4.4, M6: 4.4, M12: 4.9 TFT normal HR and temperature normal except on Day 1 due to fever
DNDi-OXA-02-HAT [redacted] Intermediate stage [redacted]	Arrhythmia	D92	Not serious Mild	Resolved after 106 days	Not related to acoziborole	Received 960 mg acoziborole on 16 December 2018 Menopaused. Ongoing non-specific ST-segment depression and AV block first degree since 16 December 2018. Resolved ventricular ectopic beats and isolated atrial ectopic beats on the same day. QTcF (ms): Pre-dose: 417; H4: 406; H9: 420; D2: 419; D3: 402; D4: 401; D5: 399; D11: 409 Ca2+ level (mg/dL): At screening: 8.9, D5: 8.9; D11: 9.7; M3: 9.9 K+ level (mmol/L): At screening: 5.8, D5: 3.7, D11: 4.2; M3: 3.1 TFT normal HR and temperature normal
~~DND~~OXA001 [redacted]	Atrial fibrillation	19 days after dosing	Not serious Moderate	Required treatment (sotalol 80 mg OD; enoxaparin 0.6 mL OD for 5 days; fluindione 15 mg OD) and recovered after 17 days	Unlikely related to acoziborole	Received 40 mg acoziborole on 27 March 2013 Reported palpitations since 2008. Not on any medications. Non smoker. QTcB (ms): Baseline: 380; H1: 363; H4: 380; H9: 371; H12: 376; D2: 371; D8: 391; D11: 397. Acozi concentration (ng/mL): H1: 321; H4: 1610; H9: 1380; H12: 1420; D2: 1580; D3: 1680; D4: 1340; D5: 1230; D6: 1320; D8: 1090; D11: 1190 K+ level (mmol/L): At screening: 4.5, D11: 3.8 (NCS), at AE onset: 4.6 TFT normal HR & body temperature normal
DNDiOXA001 [redacted]	Presyncope	1 hour after dosing	Not serious Mild	Resolved spontaneously immediately	Not related to acoziborole	Received acoziborole 240 mg on 04 October 2013 No known medical history QTcB (ms): Baseline: 367; H1: 394; H4: 375; H9: 387; H12: 383; D2: 372; D8: 396; D11: 400. Acozi concentration (ng/mL): H1: 1340; H4: 6620; H9: 7460; H12: 7640; D2: 7270; D3: 6750; D4: 6560; D5: 5910; D6: 4920; D8: 4150; D11: 3350 K+ level (mmol/L): At screening: 4.3; H0: 4.7; D3: 4.7. TFT normal HR and temperature normal
DNDiOXA001 [redacted]	Presyncope	4 days after dosing	Not serious Moderate	Resolved spontaneously immediately	Not related to acoziborole	Received acoziborole 320 mg on 04 November 2013 No known medical history QTcB (ms): Baseline: 378; H1: 379; H4: 350; H9: 355; H12: 368; D2: 377; D8: 380; D11: 360. Acozi concentration (ng/mL): H1: 1060; H4: 6560; H9: 6640; H12: 7240; D2: 6810; D3: 7230; D4: 8170; D5: 7080; D6: 6600; D8: 5760; D11: 5030 K+ level (mmol/L): At screening: 4.4; H0: 4.5; D3: 3.9; D5: 4.7. TFT normal HR normal (borderline low) and temperature normal

Abbreviations: **Acozi**, acoziborole; **D**, day; **ECG**, electrocardiogram; **g-HAT**, human African trypanosomiasis due to *Trypanosomia brucei gambiense*; **H**, hour; **HR**, heart rate; **M**, month; **OD**, once a day; **QTcB**, QT interval corrected according to Bazett's formula; **QTcF**, QT interval corrected according to Fridericia's formula; **TEAE**, treatment-emergent adverse event; **TFT**, thyroid function test.
Note: Ca2+ normal range: 8.0 – 10.3 mg/dL, and K+ normal range: 3.6 – 5.1 mmol/L in study DNDi-OXA-02-HAT and 3.9 – 5.1 mmol/L in study DNDiOXA001
Source: 5.3.5.3 Safety Data Assessment Report (SDAR).

Effects of acoziborole on QRS

The central tendency analysis did not indicate any marked effects of acoziborole on the other ECG parameters of PR interval and QRS duration, with mean (±SD) maximum changes varying from -7.4±10.7 to 2.0±11.4 ms, and from -1.4±3.9 to 0.0±3.5 ms, respectively. However, the categorical analysis showed that 19/208 (9.1%) participants had PR interval increases >220 ms, and 7/208 (3.4%) participants had PR interval increases >240 ms. Nevertheless, the individual review of these participants showed that these anomalies were not treatment-emergent, except in 1 participant. with late-stage g-HAT who presented treatment-emergent not clinically-significant and not drug-related PR interval anomalies with values >240 ms (up to 252 ms) on Day 2 and Day 3 post-dosing, and >220 ms on Day 4 and Day 5 post-dosing, which returned to baseline on Day 11.

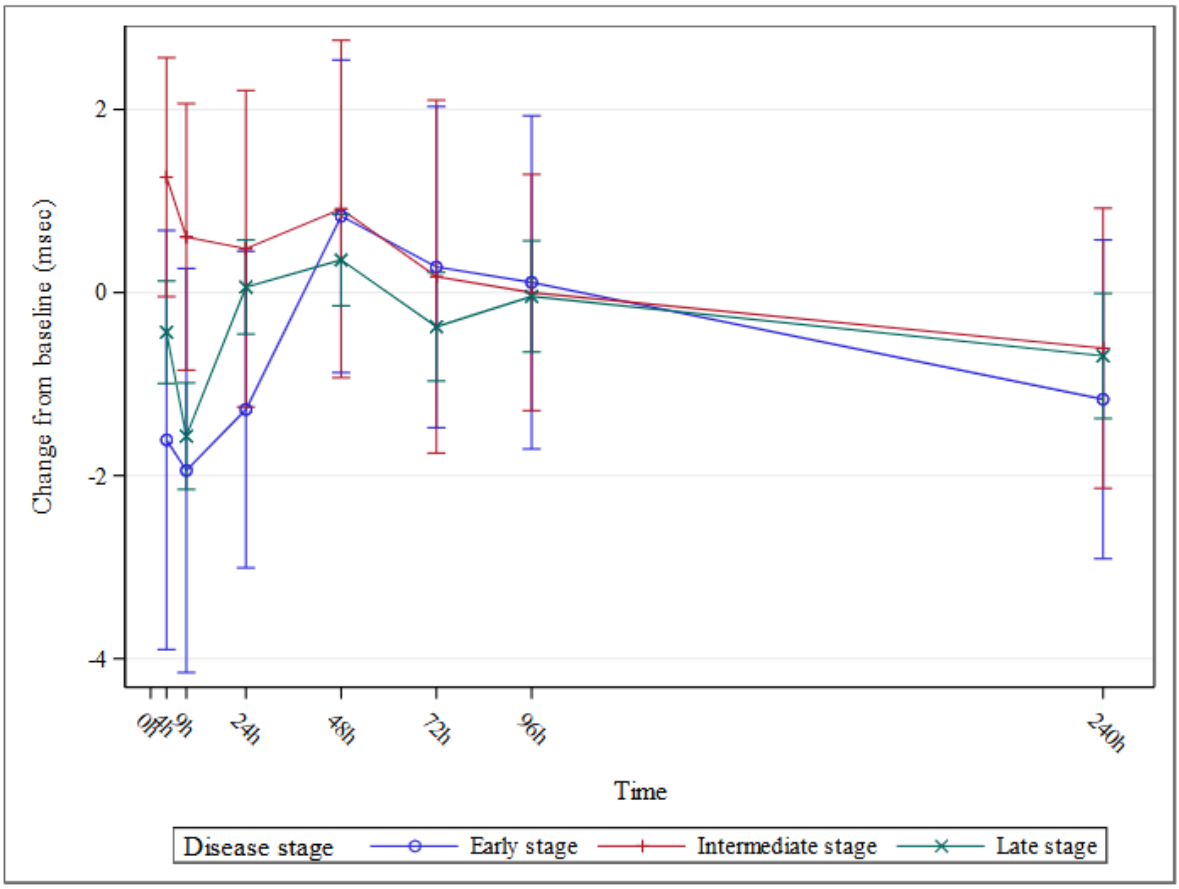


Figure 25. Analysis of central tendency of QRS duration, aggregate (msec) – Mean changes from baseline and 95% CI

5.4.9.7.2. Other study participant populations, study DNDi-OXA-04-HAT

The ECG analysis set of study DNDi-OXA-04-HAT consisted of 283 treated participants, 215 with acoziborole and 68 with placebo. All 283 participants were included in the categorical and morphological analyses. However, for 2 patients no baseline ECG was obtained and, therefore, these patients were excluded from the central tendency analysis. For 260 of the 281 treated participants included in the central tendency analysis, a matching ECG evaluation and acoziborole dry blood spot concentration was obtained and these participants were included in the concentration-response analysis. No acoziborole dry blood spot concentration was available for 21 participants and these participants were excluded from the concentration-response analysis.

At baseline, the mean (±SD) HR was 66.8±10.7 bpm and 70.0±12.1 bpm, and the mean (±SD) QTcF was 401.3±20.0 ms and 400.5±24.0 ms in participants in the acoziborole arm and placebo arm, respectively. The central tendency analysis between baseline and Day 5 did not indicate any effect of acoziborole on HR, or the duration of PR and QRS intervals. However, a decrease in QTcF was observed, with a placebo- and baseline-corrected ΔΔQTcF mean value of -11.5 ms (90% CI: [-14.4, -8.7] ms). Descriptive statistics for the absolute values and for the changes from baseline for HR are provided in Table 55. The central tendency analysis between baseline and Day 5 did not indicate any effect of acoziborole on HR, or the duration of PR and QRS intervals. However, a decrease in QTcF was observed.

Table 55. Analysis of central tendency of ECG mean heart rate (beats/min) – descriptive statistics on original values and changes from baseline

		Raw data			Change from baseline (Δ)			
Treatment	**Day**	**N**	**Mean (SD)**	**Min/Median/Max**	**N**	**Mean (SD)**	**90% CI**	**Min/Median/Max**
Acoziborole	DAY 1	213	66.8 (10.7)	47/65.0/100				
	DAY 5	213	66.4 (9.9)	45/66.0/101	213	-0.4 (8.4)	-1.3; 0.6	-30/-1.0/28
Placebo	DAY 1	68	70.0 (12.1)	44/69.0/110				
	DAY 5	68	69.1 (12.6)	47/68.0/105	68	-0.9 (8.3)	-2.6; 0.8	-19/-2.0/27

Day 1 = Baseline

Descriptive statistics for the absolute values and for the changes from baseline (Δ) for QTcF are provided in Table 56 and presented graphically in Figure 27 for the change from baseline.

Table 56. Analysis of central tendency of QTcF interval, aggregate (ms) – descriptive statistics on original values and changes from baseline

		Raw data			Change from baseline (Δ)			
Treatment	**Day**	**N**	**Mean (SD)**	**Min/Median/Max**	**N**	**Mean (SD)**	**90% CI**	**Min/Median/Max**
Acoziborole	DAY 1	213	401.3 (20.0)	344/400.0/469				
	DAY 5	213	388.5 (20.5)	342/387.0/460	213	-12.8 (13.3)	-14.3; -11.3	-51/-13.0/29
Placebo	DAY 1	68	400.5 (24.0)	363/399.5/484				
	DAY 5	68	399.0 (21.8)	353/401.0/463	68	-1.5 (13.8)	-4.3; 1.3	-38/2.0/27

Day 1 = Baseline

Following administration of acoziborole and placebo, the calculated ΔQTcF was −12.9 (90% CI: −14.3, −11.3) ms and −1.5 (90% CI: −4.3, 1.3) ms, respectively (Table 57, Figure 26). As shown in Figure 27, after administration of a single dose of 960 mg acoziborole a decrease in ΔΔQTcF was observed on Day 5 which amounted to −11.5 (90% CI: −14.4, −8.7) ms (Figure 26).

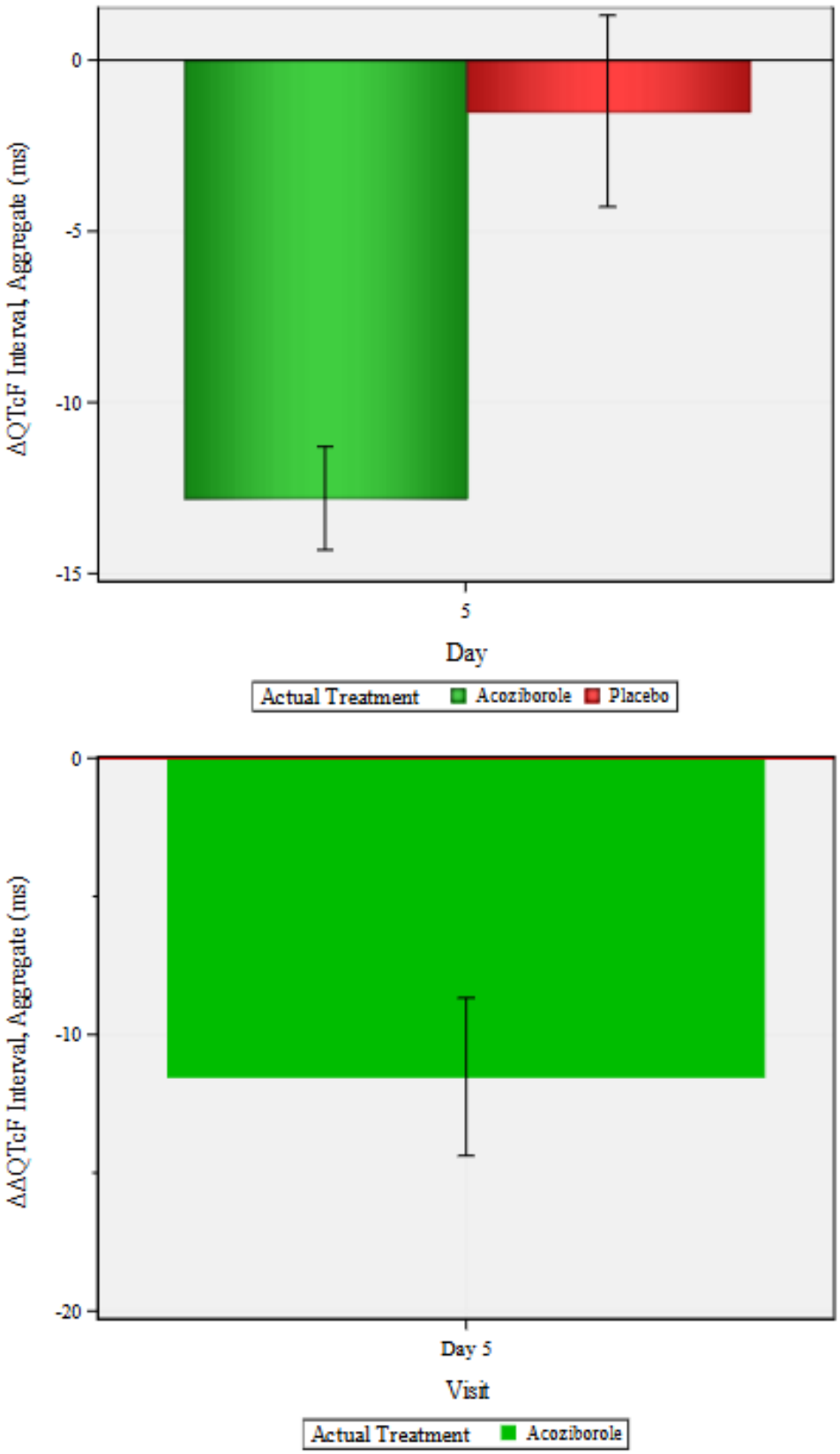


Figure 26. Analysis of central tendency of QTcF interval, aggregate (ms) – mean changes from baseline and 90% CI (top panel) and the estimated ΔΔ (change from baseline and placebo) and two-sided 90% CI at Day 5

The mean (SD) QTcF at baseline was 401.3 (20.0) and 400.5 (24.0) ms for participants treated with acoziborole or placebo, respectively (Table 60).

Table 57. Analysis of central tendency of QTcF interval, aggregate (ms) – descriptive statistics on original values and changes from baseline

		Raw data			Change from baseline (Δ)			
Treatment	**Day**	**N**	**Mean (SD)**	**Min/Median/Max**	**N**	**Mean (SD)**	**90% CI**	**Min/Median/Max**
Acoziborole	DAY 1	213	401.3 (20.0)	344/400.0/469				
	DAY 5	213	388.5 (20.5)	342/387.0/460	213	-12.8 (13.3)	-14.3; -11.3	-51/-13.0/29
Placebo	DAY 1	68	400.5 (24.0)	363/399.5/484				
	DAY 5	68	399.0 (21.8)	353/401.0/463	68	-1.5 (13.8)	-4.3; 1.3	-38/2.0/27

Day 1 = Baseline

The categorical analysis showed that none of the participants in the ECG analysis set had a QTcF value <340 ms or >500 ms on Day 5, and the ΔQTcF did not exceed 60 ms in any participant. However, a decrease in QTcF (values <360 ms) was observed in a higher proportion of participants in the acoziborole arm than in the placebo arm (4.7% [10/215] versus 1.5% [1/68], Table 61). In the acoziborole arm, the lowest post-baseline value was 342 ms, and 2 out of the 10 participants with a post-baseline QTcF value <360 ms already had a baseline QTcF <360 ms, and 1 had a value between 360 and 369 ms. The clinical significance of this QT interval shortening is currently unknown as no cardiac TEAEs were associated.

Table 58. Categorical analysis according to threshold values for QTcF changes in participants seropositive for g-HAT (Safety set) – Study DNDi-OXA-04-HAT

	Baseline QTcF				
QTcF on treatment, n (%)	**<340 ms**	**340 to 359 ms**	**360 to 369 ms**	**≥370 ms**	**Total**
Acoziborole (N = 215)					
QTcF>360 ms	0 (0.0%)	2 (0.9%)	5 (2.3%)	198 (92.1%)	205 (95.3%)
340 to 359 ms	0 (0.0%)	2 (0.9%)	1 (0.5%)	7 (3.3%)	10 (4.7%)
320 to 339 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
300 to 319 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<300 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	0 (0.0%)	4 (1.9%)	6 (2.8%)	205 (95.3%)	215 (100.0%)
Placebo (N = 68)					
QTcF>360 ms	0 (0.0%)	0 (0.0%)	6 (8.8%)	61 (89.7%)	67 (98.5%)
340 to 359 ms	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (1.5%)
320 to 339 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
300 to 319 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<300 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	0 (0.0%)	0 (0.0%)	7 (10.3%)	61 (89.7%)	68 (100.0%)

Abbreviations: g-HAT, human African trypanosomiasis due to *Trypanosomia brucei gambiense*; **QTcF**, QT interval corrected according to Fridericia's formula.

A summary of the categorical analysis for all ECG parameters investigated is provided in Table 59

Table 59. Categorical analysis , summary of abnormal values: Number (%) of participants presenting at least one value above threshold at Day 1 and /or Day 5

	Number (%) of participants presenting at least one value above threshold	
Category	Acoziborole (N=215)	Placebo (N=68)
ECG Mean Heart Rate (beats/min)		
HR<40 beats/min	0 (0.0%)	0 (0.0%)
HR>120 beats/min	0 (0.0%)	0 (0.0%)
Δ_{Rel}HR>25%	6 (2.8%)	2 (2.9%)
PR Interval, Aggregate (ms)		
PR>220 ms	2 (0.9%)	1 (1.5%)
Δ_{Rel}PR>25%	0 (0.0%)	0 (0.0%)
QRS Duration, Aggregate (ms)		
QRS>120 ms	1 (0.5%)	0 (0.0%)
Δ_{Rel}QRS>25%	0 (0.0%)	0 (0.0%)
QTcF Interval, Aggregate (ms)		
450<QTc≤480 ms	2 (0.9%)	1 (1.5%)
480<QTc≤500 ms	0 (0.0%)	0 (0.0%)
QTc>500 ms	0 (0.0%)	0 (0.0%)
30<ΔQTc≤60 ms	0 (0.0%)	0 (0.0%)
ΔQTc>60 ms	0 (0.0%)	0 (0.0%)
QTcB Interval, Aggregate (ms)		
450<QTc≤480 ms	3 (1.4%)	1 (1.5%)
480<QTc≤500 ms	1 (0.5%)	0 (0.0%)
QTc>500 ms	0 (0.0%)	0 (0.0%)
30<ΔQTc≤60 ms	1 (0.5%)	1 (1.5%)
ΔQTc>60 ms	0 (0.0%)	0 (0.0%)

N=Number of patients in the ECG analysis set by treatment group
Δ = Change from Baseline (Value - Baseline)
Δ_{Rel} = Relative Change from baseline (100x(Value-Baseline)/Baseline)

The morphological analysis by an independent cardiologist showed few treatment-emergent abnormalities (18 overall: 12 in the acoziborole arm and 6 in the placebo arm, and did not indicate any major safety concerns or notable differences between treatment arms. Of them, 4 treatment-emergent abnormalities were assessed as clinically significant, all in the acoziborole arm: 1 Participant had a “possible Wolff-Parkinson-White syndrome” congenital heart defect resulting in extra pathway for signals between upper and lower chambers on Day 5 with a non-serious TEAE of QT interval prolongation reported on Day 5, 1 Participant had a first-degree atrioventricular block >240 ms at 2 timepoints (Day 5 and at a later unspecified timepoint, during an unscheduled visit) reported as non-serious and not drug-related TEAEs, and 1 Participant had 2 events of "T-wave inversion, consider ischemia" on Day 5 (no TEAE reported). None of these events were associated with shortening of the QT interval.

Table 60. Summary of morphological analysis: Number (%) of participants presenting at least one treatment -emergent abnormality

			Number (%) of participants presenting at least one treatment-emergent abnormality	
Conclusion	Category	Abnormality Nature	Acoziborole (N=215)	Placebo (N=68)
Abnormal non clinically significant	Atrioventricular Conduction	First degree AV block	2 (0.9%)	1 (1.5%)
	Intraventricular-Intraatrial Conduction	IVCD > 110 ms and < 120 ms		1 (1.5%)
	ST Segment, T wave, and U wave	Prolonged QT or QTcF interval above Max QT/QTcF Threshold	1 (0.5%)	
		QTcF increase from baseline, > 30 ms and < 60 ms		2 (2.9%)
		T wave inversion, non-specific localized in anterior leads (V3, V4)		1 (1.5%)
		T wave inversion, non-specific localized in septal Leads (V1, V2)	1 (0.5%)	
	Supraventricular Arrhythmias	Junctional rhythm		1 (1.5%)
		Possible junctional rhythm	1 (0.5%)	
		Premature atrial complexes conducted or non-conducted	2 (0.9%)	
	Ventricular Arrhythmias	Premature ventricular complexes	1 (0.5%)	
Abnormal clinically significant	Atrioventricular Conduction	First degree AV block above 240 ms	1 (0.5%)	
		Possible WPW	1 (0.5%)	
	ST Segment, T wave, and U wave	T wave inversion, consider ischemia : other	1 (0.5%)	
		T wave inversion, consider ischemia localized in antero-septal leads (V1 - V4)	1 (0.5%)	

No TEAEs linked to ECG abnormalities or shortening of the QT interval were reported in the Safety set (N = 1206).

5.4.9.7.3. Clinical pharmacology studies

Study DNDiOXA001

Safety ECGs

In study DNDiOXA001, mean values over time in ECG parameters remained within similar range from screening to EOS and did not show differences between placebo and acoziborole cohorts regardless of the dose.

The categorical analysis showed that 47/102 (46.1%) participants on acoziborole had a post-baseline QTcB value <360 ms at any time point. The lowest post-baseline value was 334 ms. Out of these participants, 7 had already a baseline QTcB <360 ms, and 20 had a baseline QTcB between 360 and 369 ms.

In Part I, the morphological analysis showed some post-dose anomalies in 24/84 (28.6%) participants who received acoziborole, and 1/26 (3.9%) participant who received placebo:

- Twelve (12)[15] participants had a first-degree atrioventricular block at least once during the study with PR values varying between 222 and 274 ms (>ULN of 220 ms). Of them, 3 had a comparable abnormality on at least one occasion before treatment initiation.
- Five (5) participants (including the participant with placebo) had a short PR interval on at least one occasion with values from 86 to 118 ms (<LLN of 120 ms). One of them had a comparable value before treatment initiation.
- Other abnormalities were QTc increase >30 ms in 4 participants, premature ventricular complex in 2 participants, sinus arrhythmia in 1 participant, and atrial fibrillation in 1 participant.

One case of atrial fibrillation was reported in 1 Participant who received 40 mg of acoziborole. This relatively long episode was reported as TEAE, but as it occurred more than 19 days after drug

[15] In the CSR p184, the number given in brackets (ie, 13) was wrong, and should be 12.

administration, its relationship to acoziborole was considered unlikely, and the event resolved with treatment 17 days later. Moreover, 2 non-serious TEAEs of presyncope were reported in 2 participants. These events resolved within 1 min and were considered unrelated to acoziborole. These cases are more documented, see study -02 above.

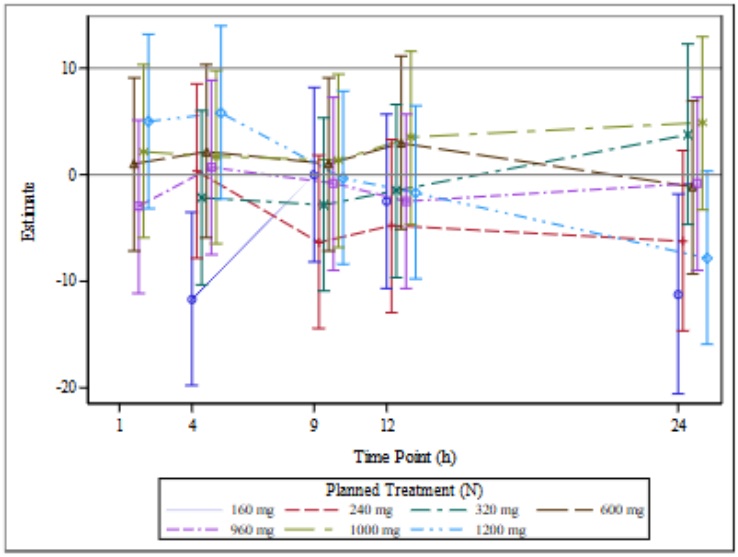
In Part IV, 1/6 (16.7%) participant had an abnormal ECG finding: 1 Participant had a first degree atrio-ventricular block with PR value between 212 and 250 ms several times during the study, but this participant had already a first-degree atrioventricular block at screening (PR value of 210 ms).

In Part VI, 2/12 (16.7%) participants had post-dose non-clinically significant ECG abnormalities: 1 Participant who received 40 mg acoziborole had a short PR interval over the study period, but this abnormality was already observed before drug administration; and 1 Participant who received 160 mg acoziborole had an isolated monomorphic premature ventricular complex on Day 2 post-dose, but the ECG was normal at recheck 4 min later.

Holter ECGs

In Part I, the analysis of 24-hour Holter ECG recordings done in 7 cohorts (160 mg, 240 mg, 320 mg, 600 mg, 960 mg, 1000 mg and 1200 mg dose levels) on Day –1 (baseline) and Day 1, and 3 cohorts (160 mg, 240 mg and 320 mg dose levels) on Day 4 showed that mean time-matched changes from baseline of QTcF values were mainly decreases (between -0.2 and -28.5 ms) in the placebo and acoziborole groups, and increases were limited (between +0.5 and +3.3 ms) in the 1000 and 1200 mg acoziborole cohorts only. The central tendency analysis on Day 1 showed that the estimated placebo-corrected baseline-adjusted ΔΔQTcF was comprised between -11.7 ms and +5.8 ms with variations within and between dose groups (Figure 27).

Figure 27. Analysis of central tendency of QTcF (ms) – Estimated ΔΔ (change from baseline and placebo) and two-sided 90% CI per dose level – Day 1



The largest estimated ΔΔQTcF was negative for doses of 160 mg (-11.7 ms), 240 mg (-6.3 ms), 960 mg (-3.0 ms) and 1200 mg (-7.8 ms), and positive for doses of 320 mg (+3.8 ms), 600 mg (+3.0 ms) and 1000 mg (+4.8 ms). It should be noted that the median t_{max} for acoziborole being between 48 and 72 hours, acoziborole plasma C_{max} was not reached during these measurements on Day 1. On Day 4, ie, 72 hours post-dose and after administration of charcoal, changes in ΔΔQTcF were also observed, mainly decreases: the largest were of -7.8 ms at 160 mg, -11.5 ms at 240 mg, and -7.3 ms at 320 mg. But, at this time point, there was no data at doses higher than 320 mg,

preventing the performance of a proper dose-response analysis. Similar results were observed for QTcB, QTcP and QTcI.

Digitalized triplicate ECG measurements were also performed on Day 8, Day 11, Visits 1, 3, 5 and 7 for the 600, 960, 1000 and 1200 mg dose level cohorts. The results showed that ΔQTcF values were mainly decreases (between -0.2 and -11.7 ms) in both study groups: up to -4.8 ms at Visit 5 with placebo, and -11.7 ms on Day 8 with 1000 mg of acoziborole; while increases were limited: up to +6.3 ms on Day 11 with placebo, and +4.0 ms at Visit 7 with 960 mg of acoziborole (see 5.3.3.1 Study DNDiOXA001 CSR [Table 14.3.8-8]). Following the central tendency analysis, the largest estimated ΔΔQTcF were negative for all acoziborole doses: -7.7 ms on Day 11 with 600 mg, -13.5 ms on Day 11 with 960 mg, -11.8 ms on Day 8 with 1000 mg, and -12.7 ms on Day 11 with 1200 mg (see 5.3.3.1 Study DNDiOXA001 CSR [Table 14.3.8-1]). No dose effect was observed at the doses between 960 and 1200 mg.

The categorical analysis showed some post-dose abnormalities. Post-baseline PR values >200 ms were reported in some participants who received acoziborole: 7 participants on Day 1, 4 participants on Day 4, and 3 participants between Day 8 and follow-up Visit 7. In participants who received placebo, 1 participant had a QRS >110 ms, 1 participant had QTcF between 450 and 500 ms and 1 participant had QTcP between 450 and 500 ms, all on Day 1 (post-dosing), and 1 participant had PR >200 ms after Day 8. No post-baseline QTcF, QTcB, QTcP and QTcI values >450 ms and no QTc prolongation >30 ms were reported with acoziborole throughout the study. However, 10/42 (23.8%) participants on acoziborole had a post-baseline QTcF value <360 ms and ≥340 ms at any time point (see 5.3.3.1 Study DNDiOXA001 CSR [Appendix 16.2.8.4.1]). The lowest post-baseline value was 345 ms. Out of these participants, 4 already had a baseline QTcF <360 ms, and 1 had a baseline QTcF between 360 and 369 ms.

Study DNDi-OXA-03-HAT

In study DNDi-OXA-03-HAT, all 6/6 (100%) participants had a post-baseline decrease of QTcF, the values remained >360 ms and ≤450 ms at all time points (screening, pre dose and 240h after dose). The lowest post-baseline value was 365 ms. No TEAEs related to ECG parameters were reported.

Subject ID	Sex/ Age	Treatment	Visit	Time point	Sample Date	Sample Time	Ventricular Rate (HR) (bpm) Value	Ventricular Rate (HR) (bpm) Change	QT Interval (msec) Value	QT Interval (msec) Change	QTcF Interval (msec) Value	QTcF Interval (msec) Change
[redacted]		[14C]-Acoziborole	SCREENING		10FEB2020	14:14	58		406		401	
			DAY 1	PRE-DOSE	24FEB2020	09:21	63		382		389	
			DAY 11	240 H	05MAR2020	09:50	74	11	362	-20	388	-1
		[14C]-Acoziborole	SCREENING		17FEB2020	10:35	57		390		385	
			DAY 1	PRE-DOSE	24FEB2020	09:25	52		383		365	
			DAY 11	240 H	05MAR2020	09:57	83	31	334	-49	373	8
		[14C]-Acoziborole	SCREENING		10FEB2020	09:29	42 L		437		389	
			DAY 1	PRE-DOSE	24FEB2020	09:30	49		407		382	
			DAY 11	240 H	05MAR2020	10:04	62	13	395	-12	400	18
		[14C]-Acoziborole	SCREENING		10FEB2020	11:12	61		422		426	
			DAY 1	PRE-DOSE	24FEB2020	09:34	66		405		418	
			DAY 11	240 H	05MAR2020	09:22	69	3	387	-18	406	-12
[redacted]		[14C]-Acoziborole	SCREENING		17FEB2020	09:55	55		398		387	
			DAY 1	PRE-DOSE	24FEB2020	09:38	59		387		386	
			DAY 11	240 H	05MAR2020	10:18	65	6	382	-5	394	8
		[14C]-Acoziborole	SCREENING		17FEB2020	10:12	62		401		406	
			DAY 1	PRE-DOSE	24FEB2020	09:41	57		373		368	
			DAY 11	240 H	05MAR2020	10:25	63	6	360	-13	366	-2

Note: All subjects were planned to receive an oral dose of 960 mg [14C]-Acoziborole (NMT 1000 nCi [37 KBq] 14C) as 4 × 240 mg capsules.
Reference Ranges: Ventricular Rate 45-100 bpm, QT Interval 200-550 msec,QTcF Interval: NA-450 msec, PR Interval 120-220 msec, QRS Duration NA-120 msec, QRS Axis -30° to 100°.
Baseline is defined as Day 1, Pre-dose. L = Below reference range. SR = Sinus Rhythm.

Study DNDi-OXA-07-HAT

In study DNDi-OXA-07-HAT, ECGs were reviewed from screening, D-1, D9, D11, D22 and at EoS (D28-31). Most participants (18/20, [90%]) had a post-baseline decrease of QTcF, all values were >360 ms and ≤450 ms at all time points. The lowest post-baseline value was 367 ms. One participant (5.0%) reported non-clinically significant abnormalities in ECG parameters post-drug administration in Period 1 (before acoziborole administration on Day 12): These abnormalities were PR above the normal range (208 ms on Day 9 and 204 ms on Day 11 for an upper limit of 200 ms). PR value was reported within normal range at subsequent visits with value of 186 ms on Day 22 and 200 ms at EoS. At screening, this participant reported already PR value above the normal range (202 ms). These abnormalities were considered as not clinically significant.

Table 61. Descriptive statistics for QTcF (msec) – Observed values and changes from baseline – Safety analysis set

		Observed values						Changes from baseline							
											95% CI				
Period	Day	N	Mean	SD	Min	Median	Max	N	Mean	SD	95% CI LB	UB	Min	Median	Max
Screening		20	400.6	18.6	363	403.0	438	0	-	-	-	-	-	-	-
1	Day -1	20	398.9	15.7	357	400.5	426	0	-	-	-	-	-	-	-
	Day 9	20	405.1	15.0	376	405.0	437	20	6.2	10.9	1.1	11.3	-20	7.0	27
2	Day 11	19	400.2	15.6	381	396.0	444	19	-0.9	13.6	-7.5	5.6	-29	0.0	28
	Day 22	19	394.3	12.7	367	396.0	420	19	-6.8	9.4	-11.3	-2.3	-26	-6.0	7
EoS		20	390.4	14.4	367	391.5	421	20	-10.2	11.4	-15.5	-4.8	-27	-12.0	10

95% CI LB = 95% confidence interval lower bound, 95% CI UB = 95% confidence interval upper bound

Summary: After administration of acoziborole to participants in study -02, most of them experienced a QT-shortening compared to baseline. The shortening of QTcF interval was seen already at 4 hours post dose (mean all participants -5,5 ms; SD 9,7) and was most pronounced at 9 hours post dose (mean all participants -11,2 ms; SD 11,9). A transient increase in heart rate after administration of acoziborole had its peak at 9 hours post-dose (ΔHR of 13.3 bpm). During the ECG observation period up to 240 hours (11 days) the QT-interval remained decreased compared to baseline. At 240 h the mean shortening of the QT interval in all participants was -10,3 ms (SD 12,2). Given the long half-life of acoziborole (12 days), it can be expected that acoziborole induced QT-shortening remains longer than the observation period in this study. There was a trend that the participants with early-stage of g-HAT experienced a more pronounced decrease from baseline compared to the other participants, however, this group included only 18 participants compared to the late-stage group that included 166 individuals and the difference might be driven by individual variations.

Arrythmia was reported on D92 in one participant in study -02 with a history of ST-segment depression and first-degree AV-block. No ECG information has been presented at the time of arrythmia. No other events of arrhythmia have been reported.

In study -04, ECG analysis was executed in a subset of 283 participants (n=215 acoziborole; n=68 placebo) at baseline and on Day 5. On Day 5 the placebo group was presented with a mean shortening of QTcF interval of -1,5 ms (SD 18,8), and a clear decrease was observed on Day 5 in the participants that received acoziborole (mean -12,8 ms; SD 13.3).

As described in section 2, QT-shortening was observed in the pharmacology studies, however, no dose-depending pattern could be identified. In study -001 one case of artrial fibrillation was reported on D19 in a participant receiving 40 mg acoziborole. The difference in QT-interval compared to baseline was: 1h (-17 ms), 4 h (+/- 0), 9h (-9 ms), 12h (-4 ms), D2 (-9 ms), D8 (+11 ms), D11 (+17 ms).

There is limited information on drug-induces shortening of the QT-interval. However, there are associations described between drug-induced QT-shortening and drug-induced ventricular fibrillation, there is however no agreement at present on appropriate limits when characterising drug-induced QT

shortening (Malik et al 2016). In the ESC guidelines ventricular arrhythmias 2022, the panel proposed two QTc cut-off threshold for diagnosis: A QTc ≤320 ms alone, or B a QTc ≤360 ms combined with a family history of SQTS. Limits used for pathological and clinical concerns to evaluate congenital or acquired short QT syndrome are 330-340 ms. Depending on the baseline QT interval for each patient, a shortening might be of clinical relevance. The data presented in the studies support that acoziborole induce a QT-shortening, although an individual variation was noted, which should be clearly described in the product information.

5.4.9.8. Physical Examination

Participants with g-HAT

Reported physical examination findings in the Treated set (N = 208) of participants with g-HAT suggested a general improvement (ie, reduction in abnormalities) in all participants during the study.

The incidence of swollen cervical lymph nodes, which was greater than 50% (115/208 [55.3%]) at baseline due to the disease, decreased over time with an overall incidence of 41.9% (83/198) on Day 15 (EOH) and continued throughout the study, with an incidence of 32.5% (67/206) at Month 3, 19.5% (40/205) at Month 6, 10.4% (21/202) at Month 12 and 1.5% (3/200) at Month 18.

The incidence of other reported abnormalities at baseline also decreased during the study: scratch marks on the skin (from 32.2% at baseline to 24.7% at EOH, 11.6% at Month 3 and 1.5% at Month 18), abnormal palpation and percussion of the abdomen (from 10.1% at baseline to 5.1% at EOH, 4.9% at Month 6 and 1.5% at Month 18), and stiff nape (from 5.8% at baseline to 0.5% at EOH, and 0% from Month 6 onwards).

The findings reported in this section is most likely related to the disease rather than reflecting possible adverse events.

Other study participant populations

In study DNDi-OXA-04-HAT, the percentage of participants seropositive for g-HAT presenting signs and symptoms at baseline decreased from 45.7% (551/1206) to 7.8% (94/1206) on Day 5 (with similar percentages in the acoziborole and placebo arms). This decrease was maintained at Month 1 (9.6% [116/1206]) and Month 4 (5.6% [68/1206]).

Clinical pharmacology studies

No other clinically significant abnormal findings were reported in physical examinations after administration of acoziborole.

5.4.9.9. Neuropsychiatric Examination

Participants with g-HAT

A general improvement in neuropsychiatric observations was found during the study DNDi-OXA-02-HAT, mainly in participants with late-stage g-HAT; few abnormalities were reported at any time points in any participants with early- or intermediate-stage g HAT.

Psychiatric observation

1/41 (2.4%) participant with early- or intermediate-stage g-HAT presented with mild/moderate behavioural disturbances from baseline to EOH.

In participants with late-stage g-HAT the incidence of abnormalities reported in >5% of participants at baseline decreased during the study as follows:

- Behavioral disturbances (mild/moderate): from 19.8% at baseline to 3.8% at EOH and 0.6% (1 participant) in Month 18.
- Flow of words: incidence of reduced verbal flow decreased from baseline (17.4%) to EOH (3.8%) and Month 18 (0.6%, 1 participant); and incidence of exaggerated verbal flow decreased from baseline (7.2%) to EOH (1.3%) and Month 18 (0%).
- Psychomotor slowing: from 16.8% at baseline to 5.1% at EOH and 0% from Month 6 onwards.
- Depressed mood: from 6.0% at baseline to 0.6% (1 participant) at EOH and 0% from Month 6 onwards.

Almost all other abnormalities in participants with late-stage HAT were reported in ≤5% of participants at baseline and throughout the study. The exception was exalted mood, which increased slightly from an incidence of 4.8% at baseline to 6.0% at Day 5 before decreasing during the rest of the study; this abnormality was no longer reported at Month 18.

Higher functions

1/41 (2.4%) participant with early- or intermediate-stage g-HAT presented with impaired memory at Month 6 only.

In participants with late-stage g-HAT, the incidence of abnormalities reported in >5% of participants at baseline, decreased during the study as follows:

- Lethargy: from 17.4% at baseline to 2.5% at EOH and 0% from Month 3 onwards.
- Impaired memory: from 12.6% at baseline to 0.6% (1 participant) at EOH and 0% at Month 18.
- Dysarthria: from 11.4% at baseline to 4.5% at EOH and 0.6% (1 participant) on Month 18.
- Temporal disorientation: from 9.0% at baseline to 1.3% at EOH and 0% from Month 12 onwards.
- Praxis: from 9.0% at baseline to 2.5% at EOH and 0% from Month 6 onwards.

Cranial nerves

All participants (41/41 [100%]) with early- or intermediate-stage g-HAT had normal findings at all time points during the study. In participants with late-stage g-HAT, the incidence of normal cranial nerve findings increased from 95.2% at baseline to 98.7% at EOH, and by Month 18 all but 1 participant had normal findings (166/167, [99.4%]).

Mobility

All participants (41/41 [100%]) with early- or intermediate-stage g-HAT had normal findings at all time points. In participants with late-stage g-HAT, no abnormalities were reported for any item by Month 18. The incidence of abnormalities reported in >5% of participants at baseline decreased during the study as follows:

- Involuntary movements (mild/moderate): from 22.2% at baseline to 8.3% at EOH and 0% from Month 3 onwards.

- Difficulty with or help required for walking: from 25.7% at baseline to 10.8% at EOH and 0% at Month 18.
- Reduced segmental motor control (in any one limb): from 8.4% at baseline to 3.8% at EOH and 0% from Month 3 onwards.
- Reduced tonicity: from 7.2% at baseline to 2.5% at EOH and 0% from Month 6 onwards.

Motor coordination

The only abnormality reported in >5% of participants with early- or intermediate-stage g-HAT at baseline was tremor, the incidence of which decreased from 7.3% at baseline to 0% at EOH. By Month 18, no abnormalities were reported for any item.

In participants with late-stage g-HAT, one 1/167 (0.6%) participant presented with tremor by Month 18. Decreases in the incidence of abnormalities reported in >5% of participants at baseline were as follows:

- Romberg's test: incidence of impaired balance decreased from 19.2% at baseline to 3.8% at EOH and 0% from Month 12 onwards.
- Abnormal rapid alternating movements: from 16.8% at baseline to 4.5% at EOH and 0% from Month 12 onwards.
- Tremor: from 36.5% at baseline to 17.2% at EOH, 4.2% by Month 3 and 0.6% (1 participant) by Month 18.

Primitive reflex

In participants with early- or intermediate-stage g-HAT, the incidence of palm-chin reflex decreased from 2.4% (1/41) at baseline to 0% at EOH until Month 18.

In participants with late-stage g-HAT, the incidence of palm-chin reflex also decreased from 26.3% at baseline to 18.5% at EOH, 5.5% at Month 3 and 0% at Month 18.

Sensation

All participants with early- or intermediate-stage g-HAT had normal findings at all time points.

In participants with late-stage g-HAT, no abnormal findings were reported in >5% of participants at baseline or any time point during the study; at Month 18 no abnormalities were reported.

Other study participant populations

No specific neuropsychiatric examination was performed in study DNDi-OXA-04-HAT.

Clinical pharmacology studies

No neuropsychiatric findings were reported.

5.4.10. Post-marketing experience

Not applicable

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

The safety database constitutes mainly of two phase II/III studies executed in Guinea and DRC (DNDi-OXA-02-HAT, DNDi-OXA-04-HAT). Supportive safety data from three phase I studies have been presented (DNDiOXA001, DNDi-OXA-03-HAT, DNDi-OXA-07-HAT).

DNDi-OXA-02-HAT is a single-arm, multicenter, open label study evaluating efficacy and safety. The study included only participants with parasitologically confirmed early, intermediate or late-stage g-HAT. A single oral dose of acoziborole 960 mg were administered to 208 participants ≥15 years at fasting state. The study duration was 18 months. The study is considered as the pivotal study for this application.

DNDi-OXA-04-HAT is a placebo-controlled, double-blind study including participants seropositive to g-HAT (not parasitologically confirmed) to evaluate safety. A single oral dose of either acoziborole 960 mg (n=906) or placebo (n=300) were administered to participants ≥15 years at fasting state. The study duration was 4 months.

Adverse events

DNDi-OXA-02-HAT

In study -02, at least one TEAEs (after the date of administration of acoziborole up to study end) were reported in 74% of the participants, of which 13,5% were severe and 13,9% were considered related to acoziborole by the investigator.

Nervous system disorders were reported in 31% in total (early/intermediate 34%; late 31%) and infections and infestations at a frequency of 31% (early/intermediate 20%; late 34%). The most reported PT in all stages of g-HAT were associated with the diagnostic lumbar puncture: procedural pain (25%) and procedural headache (15%).

Other commonly reported PTs for the entire study population were headache (25%), pyrexia (15%) and malaria (14%). Headache has been proposed to be included as an ADR in the product information. The PTs considered related to treatment by the investigator that were reported in ≥2 participants included pyrexia, asthenia, dyskinesia, tremor, headache, abdominal pain, decreased appetite. The following PTs considered related to treatment were reported once: chills, dizziness, nausea, vomiting and pruritus. All drug related events were mild or moderate at intensity and resolved. The events was proposed by the Applicant to be included in the ADR table in section 4.8 of the SmPC. Given the challenges to evaluated possible ADRs in a single arm study including participants with a severe disease, and that no other safety profile is presented in the placebo-controlled study -04, it can be accepted to include these PTs in the SmPC section 4.8.

It is noted that more participants (n=127) reported TEAEs during the initial two weeks after administration of the treatment during hospitalization than at the time from hospitalization up to EoS (18 months) where 99 participants reported TEAEs. This suggests that more events occurred in relation to procedural complications and the treatment with acoziborole, and that it is easier to observe any TEAEs when participants are at hospital instead of home. In total, 44 severe TEAEs were reported by 28 participants, of which anaemia (1,9%), malaria (1,9%), headache (1,4%) were most reported. Anaemia can be a clinical symptom of g-HAT and is more likely caused by the disease than by the treatment.

In study -02 some of the participants had a change from baseline in TSH (8%), T3 (5%) and T4 (10%) on D11. The pharmacological studies suggested that acoziborole might have an impact on the thyroid

function based on changes in thyroid parameters, where two participants receiving 160-240 mg acoziborole reorted TEAE of decreased TSH togehter with increased T3 and/or T4 67-68 days after dosing. The participants had no clinical signs and the parameters returned spontaneously to baseline within 6-12 weeks.

In study -02 four events of death were reported (ascending peripheral neuropathy, poisoning, extrapulmonary tuberculosis and post-surgery acute pulmonary oedema), all with late-stage g-HAT. None of the events of death were considered related to acoziborole by the investigator, a conclusion that can be endorsed since the events had other more likely causes to the fatal outcome.

DNDi-OXA-04-HAT

In study -04, at least one TEAE was reported in 21,5% participants in the acoziborole group, and in 23% in the placebo group. A slightly higher frequency of TEAEs were reported in female than men in both the acoziborole group (24,6% vs 18%) and the placebo group (27% vs 18%). The similar frequency between the groups suggest that the difference is not related to treatment. During the five days of hospitalization a similar frequency of TEAEs were reported in the two groups (acoziborole 13,7%; placebo 12,7%), the same pattern was noted the following almost 4 months up to EoS where 11,7% in the acoziborole group and 15% of the participants in the placebo group reported TEAEs. The most frequently reported PTs were headache (acoziborole 5,8%; placebo 2,7%), malaria (3,8% vs 4,7%) and abdominal pain (2,5% vs 3%). Most of the events were mild to moderate at intensity. Headache and abdominal pain are included as ADRs in the product information at frequency common and uncommon, respectively.

Among the 26 reported events of severe TEAEs in study -04, increased potassium was the most reported PT in both the acoziborole (n=8) and the placebo group (n=3). According to the investigator none of these were considered related to treatment. The three events of increased potassium in the placebo group were reported on D4, D53 and D121. The event reported on D4 had a duration of 4 days. Three of the events reported in the acoziborole group occurred D123 and based on timepoint it can be agreed that these are not likely associated with treatment. Iin the acoziborole group, severe TEAE of increased potassium were reported in three participants on D5 and in one participant on D31, which was explained by the increased levels already at screening.

The most frequently reported TEAEs considered related to treatment were headache (3.1% in the acoziborole group vs 1.7% in the placebo arm), abdominal pain (1.5% vs 2.0%), fatigue (0.9% vs 1.7%), dizziness (0,6% vs 0,3%), pyrexia (0,2% vs 0%), hot flush (0,3% vs 0%), insomnia (0,2% vs 0%), decreased appetite (0,7% vs 0,3%) and nausea (0,6% vs 0,7%). All were mild or moderate at intensity.

One event of death (malaria) was reported in the study (placebo group).

The single event in study -04 of prolonged QT interval as considered related to treatment is a divergent observation, as the general observation in this study was an overall shortening of QT-interval in participants treated with acoziborole compared with placebo (see the part electrocardiogram).

It can be agreed to include a general supportive statement from this study in section 4.8 in the SmPC including information on study size and study population. The single event in study -04 of prolonged QT interval as considered related to treatment is a divergent observation, as the general observation in this study was an overall shortening of QT-interval in participants treated with acoziborole compared with placebo (see section electrocardiogram).

Anaemia was reported in both clinical studies (-02 n=7; -04 n=4). Since trypanosomiasis can cause anaemia, the events are probably more likely related to g-HAT than to the treatment.

None of the participants discontinued the clinical studies or the pharmacological studies due to adverse events.

Simulations for paediatric population clearly indicate that exposure to the drug increases as body weight decreases; a similar phenomenon is therefore expected also in adult population. From the data provided, the safety profile in patients <40 kg seem similar to the general patient population enrolled in the studies.

Pregnancy and breastfeeding

In the clinical studies, pregnancy was an exclusion criteria and pregnancy tests were performed before treatment at study visits. It is noted that hormonal contraceptive was offered to the female participants in the clinical studies, which is questioned since acoziborole can reduce the effectiveness of hormonal contraceptives. None of the female participats reported using hormonal contraception before inclusion or during the study. According to the Applicant, it was specified that contraceptive protection through condom use or sexual abstinence was required to participate in both clinical studies. In study -02 were 7 pregnancies reported of which 5 resulted in healthy newborns. The remaining two pregnancies had fatal outcomes due to stillbirth and sepsis. In study -04 were 8 pregnancies reported in the acoziborole group of which 6 resulted in healthy newborns. The remaining two pregnancies ended with spontaneous abortion and breech presentation with umbilical cord prolapse.

The Applicant propose to include information about the reduced efficacy of hormonal contraceptives in section 4.6 of the SmPC and recommend a barrier contraception method during the first three months of treatment. This is endorsed. Regarding pregnancy, there is very limited clinical data. Notably, the preclinical data have shown reproductive toxicity and that acoziborole crosses the placenta. On the other hand, vertical transmission of the trypanosome infection occurs, and the late-stage g-HAT disease can be lethal to the mother. It is therefore proposed in the product information to not use Acoziborole during pregnancy unless the woman requires immediate therapy and no other option is available.

The preclinical data has showed that acoziborole is excreted in milk with a risk for accumulation. No data from exposure of acoziborole at breastfeeding in the clinical studies has been presented and a risk for the suckling child cannot be excluded. Due to the risk of accumulation, it is suggested to not use Acoziborole during breastfeeding which is described in the SmPC.

Electrocardiogram

In study -02, most participants experienced a shortening of the QT-interval compared to baseline. The decrease was observed already at 4 hours post dose (mean all participants -5,5 ms; SD 9,7) and was most pronounced at 9 hours post dose (mean all participants -11,2 ms; SD 11,9). A transient increase in heart rate after administration of acoziborole had its peak at 9 hours post-dose (ΔHR of 13.3 bpm). During the ECG observation period up to 240 hours (11 days) the QT-interval remained decreased compared to baseline. At 240 h the mean shortening of the QT interval in all participants was -10,3 ms (SD 12,2). Given the long half-life of acoziborole (12 days), it can be expected that acoziborole induced QT-shortening remains longer than the observation period in this study.

In study -04, ECG analysis was executed in a subset of 283 participants (n=215 acoziborole; n=68 placebo) at baseline and on Day 5. On Day 5 the placebo group was presented with a mean shortening of QTcF interval of -1,5 ms (SD 18,8), and a clear decrease was observed on Day 5 in the participants that received acoziborole (mean -12,8 ms; SD 13.3).

As described in section 2, QT-shortening was also observed in the pharmacology studies, however, no dose-depending pattern could be identified. The molecular mechanism of this effect is not understood.

There is limited information on drug-induced QT-interval shortening. However, there are associations described between drug-induced QT-shortening and drug-induced ventricular fibrillation. At present, there is no agreement on appropriate limits when characterising drug-induced QT shortening. Limits used for pathological and clinical concerns to evaluate congenital or acquired short QT syndrome are 330-340 ms. Depending on the baseline QT interval for each patient, a shortening might be of clinical relevance. The data presented in the studies support that acoziborole induce QT-shortening, which is further described in the SmPC section 5.1. Shortening of QT interval is also included as an ADR in section 4.8 of the SmPC at frequency very common.

5.4.11.1.1. Overall assessment of available safety data

The most frequently reported events after administration of Acoziborole was QT-shortening, which occurred in most of the participants although none presented with arrythmias in the clinical studies. Headache was also a frequently reported event. Acoziborole has a long half-life (12 days) which must be taken into account both in duration of ADRs such as QT-shortening as well as its ability to interact with other substances, including hormonal contraceptives. There is no clinical information regarding pregnancy and breastfeeding. However, preclinical data suggest secretion in milk and thereby possible accumulation to the child and that Acoziborole crosses the placenta.

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3.1. and 5.4.3.4. above. A similar safety profile was observed in both study -02 and -04, and the suggested ADRs is accepted.

5.4.11.2. Conclusions on clinical safety

Overall, an acceptable safety profile has been presented in the two clinical phase II/III studies for the treatment of patients with g-HAT with acoziborole. The main clinically relevant observation is the shortening in QT-interval. However, this was not associated with serious outcomes in the clinical studies. Moreover, there is uncertainties about use in pregnancy and breastfeeding due to limited data and appropriate labelling has been instituted.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 62. Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYO3A4 (strong induction)
Important potential risks	Arrhythmia caused by shortening of QT interval
Missing information	Use during pregnancy
	Use during breastfeeding

6.1.2. Discussion on proposed safety specification

Risks considered important by the Applicant for inclusion in the list of safety concerns in the RMP are described further in Table 64, Table 65 and Table 66.

Table 63. important identified risk considered for inclusion in the list of safety concerns: Effect of Acoziborole on other drugs mainly metablized by CYP2D6 (strong inbibation) 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 dextromethorphan, desipramine, paroxetine, propafenone, atomoxetine, thioridazine) 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, praziquantel, Ibudesonide, ciclosporin, fentanyl, midazolam, quetiapine, quinine, simvastatin, tacrolimus) 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 64.Important potential risk considered for inclusion in the list of safety concerns: Arrhythemia 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 65.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 and fetal development in rabbits (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 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	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).

Table 66. Missing information considered for inclusion in the list of safety concerns: Use during lacation.

Use during lactation	
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.

Summary of safety concerns

Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction) has been proposed by the Applicant to be included in the summary of safety concerns as an important identified risk. There is information in the SmPC that acoziborole is a strong inhibitor of CYP3A4 and that acoziborole can increase the exposure of concomitant CYP2D6 substrates in section 4.4 and 4.5. In addition, the SmPC includes information that acoziborole can induce CYP2C8, CYP2C9, CYP2C19, CYP1A2, CYP2B6, and UGT enzymes is also described. The potential of acoziborole to strongly inhibit or induce several important enzymes and thereby reduce or increase the efficacy of other concomitant treatments are highly important information that must be given to both the patient and practitioner. Risk minimization measures to ensure this is of highly importance and it is therefore agreed to include this as an important identified risk.

Arrythmia caused by shortening of QT-interval has been proposed to be included in the summary of safety concerns as an important potential identified risk in the summary of safety concerns. This can be agreed since a general shortening of QT-interval was observed in most participants in the clinical studies after administration of acoziborole, and further information on possible arrythmia caused by the acoziborole induced shortening of QT-interval is therefore requested.

The Applicant has proposed to include use during pregnancy and breastfeeding as missing information. The wording was changed from lactation to breastfeeding. There is no or very limited information on the use of acoziborole in those populations from the clinical studies since pregnancy and breastfeeding was exclusions criteria. It is proposed that acoziborole should not be used during pregnancy unless the clinical condition of the woman with late-stage g-HAT requires treatment prior to delivery. Acoziborole is excreted in milk in preclinical studies and a risk to the suckling child cannot be excluded, breastfeeding at treatment must take the benefit of therapy for the mother and the benefit of breastfeeding fort the child into account. The outcomes and follow-up are highly important if cases of pregnancy and breastfeeding will occur and it is therefore agreed to include use

during pregnancy and breastfeeding as missing information.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

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 ADRs and signal detection in periodic safety reports. The WHO will collect pharmacovigilance cases from the g-HAT centers with local support of NSSCPs. Specific targeted follow-up forms adapted from WHO pharmacovigilance forms will collect safety information on acoziborole that addresses the risks and missing information described in [Part II Module SVIII].

Practically, specific targeted forms will collect information for all adverse events (AEs), any co-medication prescribed within 3 months following acoziborole administration, pregnancy, breastfeeding status (initial and follow-up report) and a pregnancy form to document any confirmed pregnancy or breastfeeding after acoziborole exposure.

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

In addition, the applicant has proposed the following additional pharmacovigilance activities:

Table 67. 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 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.	Primary objectives: • Describe the frequency of any AEs in the 3-month period following acoziborole treatment, overall and stratified by concomitant use of potentially interacting medicines. Potentially interacting medicines are defined as medicines mainly metabolized by	• Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction) • Use during pregnancy • Use during lactation	Protocol submission to PRAC Protocol endorsement by PRAC Data extraction (WHO database delivery to MAH) Start of data analysis Final report of study results	Estimated Q2 2026 Estimated Q4 2026 Estimated Q1 2030 Estimated Q2 2030 Estimated Q1 2031

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Planned	CYP2D6 or CYP3A4. • Describe the use of all concomitant medicines, including 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; MAH: Marketing Authorization Holder; PASS: Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; WHO: World Health Organization.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The Applicant describes their routine pharmacovigilance activities, including specific targeted follow-up forms adapted from WHO pharmacovigilance forms. These forms are not included in Annex 4 of the RMP. According to the GVP V rev 2, standard follow-up questionnaires for adverse reaction reporting are not deemed routine pharmacovigilance activities beyond adverse reaction reporting and signal detection. Therefore, the Applicant is kindly requested to remove the mentioning of the specific targeted follow-up forms adapted from WHO pharmacovigilance forms as routine pharmacovigilance activities. In respons, the Applicant has renamed the specific targeted follow-up forms into standard follow-up forms adapted from WHO pharmacovigilance forms. This is still not in line with the GVP V rev 2 and the mentioning of the should be removed form this section in the RMP. These forms may be used however, as these forms are meant for a standard follow up of reported events, these forms should be removed from the RMP**.**

6.2.2.2. Additional pharmacovigilance activities

The Applicant proposes a Category 3 PASS to further characterise the safety issues : Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction), Use during pregnancy , and Use during lactation.

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 CYP3A4in 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 adverse events (AEs) and use of any concomitant medicine in the 3-month period following 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:

Milestone	Planned date
Protocol submission to PRAC	Estimated Q2 2026
Protocol endorsement by PRAC	Estimated Q4 2026
Data extraction start (WHO database delivery to MAH)	Estimated Q1 2030
Start of data analysis	Estimated Q2 2030
Final report of study results	Estimated Q1 2031

The Applicant has included the synopsis of the protocol for the study in the Annex 3.1 of the RMP. This protocol is a detailed summary, including milestones stating the study protocol will be submitted Q2 of 2026.

As there are additional risk minimization measures in place with the key element: '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', the number of relevant events may be small for further characterization of the risk 'Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)'. This is partly due to the unknown study size and the possibility no drugs mainly metabolized by CYP2D6 or CYP3A4 or traditional medications will be used in the 3 months following the use of acoziborole. Concerning the study size, the Applicant states in the summary that the study will include all patients treated with acoziborole for g-HAT available in the WHO acoziborole active pharmacovigilance database, however, this is thus depended on the actual number of patients. As the WHO has the goal of eliminating g-HAT by 2030, in the countries most afflicted with g-HAT often experience socio-political conflicts and competing health crises it is challenging to estimate incidence, lastly the supply of acoziborole in the affected countries is dependent on site capabilities in training medical personnel adequately. These limitations are acknowledged. Upon request the Applicant has provided an estimation of the participants inclusion based on previous experience with fexinidazole. For the fexinidazole PASS 993 patients were included, while WHO reported a total of 3332 g-HAT cases, approximately 30%. The Applicant, therefore, estimates an inclusion of approximately 30% of all WHO reported g-HAT cases. The Applicant further describes multiple factors that can influence this sample size, such as decrease in cases overall, a difference in study periods (2020-2024 for fexinidazole, and 2027-2029 for acoziborole), but also the potentially more rapid and wider uptake of acoziborole. Furthermore, the Applicant has provided the expected statistical precision (95% CI), which is appreciated.

Upon request, the Applicant has included the evaluation of the patient card effectiveness in the primary objective of the PASS. The Applicant explained, however, that an interim report of the study will not be feasible as the data transmission is complex and follows a multi-tiered pathway from the district level to the provincial level, then national and ultimately up to the WHO level. After the data transmission, the WHO is responsible for the data validation and cleaning, which may extend several months as it often requires direct engagement with the original data reports to resolve data

discrepancies. Based on this, the Applicant states that continuous data extraction is not viable activities can be carried out. It is assumed that the data transmission is continuous and therefore the line listings can be made available by the WHO every 6 months, as this is already the case for fexinidazole which has the same PV process in place.

6.3. Plans for post-authorisation 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

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 68. Planned routine risk minimisation measures

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:** SmPC: Section 4.3, section 4.4, section 4.5. PL: Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Contraindication in patients taking antiretroviral drugs such as lopinavir, ritonavir, atazanavir and darunavir, or taking praziquantel. • Recommendation for dose adjustment, monitoring for loss of efficacy or increase in effects in case of co-administration with CYP3A4 and CYP2D6 substrates are included in SmPC section 4.5. • List of medicines that can have potential DDI with Acoziborole Winthrop is provided in PL section 2. **Other routine risk minimization measures beyond the Product Information:** Patient card explaining DDI to be provided by healthcare staff at the time of the treatment.
Arrhythmia caused by shortening of QT interval	**Routine risk communication:** SmPC: Section 4.3, section 4.4. PL: Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Contraindication in patients with familial short QT syndrome in in SmPC section 4.3 and in PL section 2. • Recommendations for use in patients already treated with a drug known to shorten the QT interval or with risk factors (such as familial history of syncope, sudden death, etc.) are included in SmPC section 4.4. • Caution during the first month after treatment with acoziborole if a concomitant medication known to shorten the QT interval is prescribed in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information:**

Safety concern	Routine risk minimization activities
	Not applicable
Use during pregnancy	**Routine risk communication:** SmPC: Section 4.6. PL: Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations for use during the specific trimester of the pregnancy are included in SmPC section 4.6. • Precautions to be taken in case of a possible or confirmed pregnancy are described in PL section 2. **Other routine risk minimization measures beyond the Product Information:** Not applicable
Use during breastfeeding	**Routine risk communication:** SmPC: Section 4.6. PL: Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations for breastfeeding at the time or after the treatment are included in SmPC section 4.6. • Recommendations for breastfeeding are described in PL section 2. **Other routine risk minimization measures beyond the Product Information:** Not applicable

CYP: Cytochrome P450; DDI: Drug-Drug Interaction; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

In addition, the applicant has proposed the following additional risk minimisation measures:

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

Acoziborole will only be available in this control 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).

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 have been identified, trained and supervised by the NSSCPs. In these centers, patients are treated with the currently available HAT treatments, and their safety is supervised by HCPs formally trained for the treatment of HAT. In line with the current management of HAT in endemic countries and to secure appropriate and safe supervision of patients with this new treatment, the use of acoziborole will be provided in the identified and selected healthcare centers. In these centers the healthcare staff will be 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.

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 69. Additional risk minimization measures

Patient Card	
Objectives	To remind "patients/caregivers" and to inform other HCPs or medical referents involved in patient's care 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 diagnose 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-month post-treatment period in the context of concomitant medicines mainly metabolized by CYP26 or CYP3A4. Analysis through final PASS report.

Patient Card

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.

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), within a three months 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 to 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. Physician educational/safety advice tool:

• The Summary of Product Characteristics (SmPC).

• The Patient Card.

2. Patient educational/safety advice tool:

• The Patient Leaflet.

• The Patient Card - see description above.

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 Human African Trypanosomiasis (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 the Patient Card 3 months after Acoziborole treatment (trough visuals).

• National or World Health Organization (WHO) Pharmacovigilance system contact details to report adverse events (AEs).

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The Applicant proposed routine risk minimisation measures of addressing the risks in the SmPC and PL. In addition, the Applicant proposes additional risk minimisation measures.

6.4.2.2. Additional risk minimisation measures

The Applicant proposes a patient card to inform the patient of the risk DDI, especially for those drugs mainly metabolized by CYP2D6 or CYP3A4, and to remind not to use traditional medicines in the 3 months following the acoziborolo dosis.

The additional risk minimisation measures in the form of a patient card is acceptable for the risk 'Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)'. The patient will take the treatment in the healthcare facility, therefore the card cannot be included in the package and will be provided by the prescribing HCP. For the key element addressing the prescriber, Reminder for the Human African Trypanosomiasis (HAT) HCP to alert the patient about DDI and to give the Patient Card to the patient, the Applicant states that it is important that the HCP instructs the patient, especially those with limited literacy skills, which is acknowledged. Though the local healthcare setting in the endemic areas may be different and may not be as familiar with patient cards, it is assumed the HCPs that are trained to prescribe acoziborole, will also be trained in the use of the patient card. Nevertheless, due to the importance of the patient card, the key element addressing the prescriber is accepted as an exemption. The other key elements are acceptable as well.

Furthermore, the use of acoziborole is subjected to a controlled access and distribution program by the WHO and the National Sleeping Sickness Control Programme, which is in accordance with all other human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense treatments. The National Sleeping Sickness Control Programme oversees the healthcare centres in which treatment for HAT is provided and trains the healthcare professionals working in them. The product will be distributed through the WHO neglected tropical diseases department to NSSCPs and from there to the treatment centers treating HAT patients. This program is accepted.

6.4.2.3. Patients engagement on the risk minimisation activities

No patient experience data on risk minimisation preferences were submitted within this procedure.

6.5. RMP summary and RMP annexes overall conclusion

Pending the CHMP discussion on the safety and safety specification, the RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 24 February 2026.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed.

8. Product information

8.1. Summary of product characteristics (SmPC)

See attached edited product information including *Rapporteur assessment.*

8.1.1. SmPC section 4.1 justification

Acoziborole Winthrop has been shown to be effective at curing the disease (measured as the number of patients having no clinical signs of HAT, no detectable parasites in any fluid and a cerebrospinal fluid white blood cell count ≤ 20 cells/µl). The results showed that, after 18 months, treatment had been successful in 95.2% (159 out of 167) of people with second-stage disease and 100% (41) of patients with first- and intermediate-stage g-HAT.

8.2. Labelling

See attached edited product information including Rapporteur assessment.

8.2.1. Package leaflet (PL)

See attached edited product information including Rapporteur assessment.

8.2.2. User consultation

A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

8.2.3. Quick Response (QR) code

Not applicable

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Human African trypanosomiasis (HAT) or sleeping sickness is a neglected tropical disease (NTD) endemic in regions in sub-Saharan Africa that generally leads to the death of the patient if left untreated. The transmission of infective parasites to humans results from the bite of specific species of tsetse fly and humans constitute the epidemiologically important reservoir of the *Trypanosoma brucei gambiense* parasite.

Two clinical stages are primarily defined: Stage 1 (haemolymphatic) HAT is characterised by mild and nonspecific symptoms including intermittent fever, headache, pruritus, and lymphadenopathy, with trypanosomes being present in the blood and lymphatic system. If not diagnosed and treated, the condition progresses to stage 2 (meningoencephalitis) HAT, in which parasites invade the central nervous system. Late stage 2 patients display neurological signs including mental confusion, worsening sleep disturbances and, eventually, coma, and death.

The dosage is a single oral dose of 960 mg acoziborole for the treatment of first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* in paediatric patients ⩾12 years old and weighing at least 40 kg, and adults.

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1. of this document.

Five pharmacological therapies are included in current WHO guidelines for the treatment of HAT[16]. Most available treatments require slow intravenous infusion or intramuscular injection. The need for lumbar puncture to guide treatment choice (for example, the negligible penetration of pentamidine through the blood brain barrier restricts its effective use to first stage disease) and hospitalisation for treatment administration pose significant clinical burdens/ barriers in the usual healthcare setting in Low- and Middle-Income Countries (LMIC). The only oral treatment is fexinidazole. Directly observed administration to ensure fed conditions and a change in dose on day 5 of 10, critical to achieving effective exposures, complicates this oral regimen, Moreover, fexinidazole is not recommended in severe second stage disease:

Pharmacological therapies included in current WHO guidelines for the treatment of HAT[17]

Patient with g-HAT[//]	Clinical examination of g-HAT patients	Microscopic examination of CSF	Disease progression	Treatment		
				1st line	2nd line	Rescue
	ns	≤5 WBC/μL No tryps	First stage	Pentamidine (IM)	Ns	NECT (PO/IV)

[16] WHO Guidelines for the treatment of human African trypanosomiasis. Geneva, Switzerland. June 2024. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240096035
[17] WHO Guidelines for the treatment of human African trypanosomiasis. Geneva, Switzerland. June 2024. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240096035

Patient with g-HAT[a]	Clinical examination of g-HAT patients	Microscopic examination of CSF	Disease progression	Treatment		
				1st line	2nd line	Rescue
<6 years or <20 kg		>5 WBC/μL Tryps+	Second stage	NECT (PO/IV)	Eflornithine (IV)	NECT long (PO/IV) or Melarsoprol (IV)
≥6 years and ≥20 kg	Non-severe disease	Not needed	First stage	Fexinidazole (PO)	***LP needed*** ↓ Pentamidine (IM) or NECT (PO/IV)	NECT or NECT long (PO/IV)
	Suspicion of severe disease[b] ***LP needed***	<100 WBC/μL	Non-severe second stage	Fexinidazole (PO)		
		≥100 WBC/μL or in failed LP	Severe[b] second stage	NECT (PO/IV)	Fexinidazole (PO)	NECT long (PO/IV) or Melarsoprol (IV)

Abbreviations: **CSF**, cerebrospinal fluid; **HCP**, health care professionals; **LP**, lumbar puncture; **NECT**, nifurtimox-eflornithine combination therapy total 10 days; **NECT long**, total 14 days; **ns**, not specified; **Tryps**, trypanosomes; **WBC**, white blood cells

Source: WHO 2024 guidelines

a) Diagnosis for g-HAT confirmed by the microscopic observation of trypanosomes (T_+) in blood, lymph, or CSF if LP is performed

b) The main symptoms and signs consistent with severe meningo-encephalitic g-HAT are mental confusion, abnormal behavior, logorrhoea, anxiety, ataxia, tremor, motor weakness, speech impairment, abnormal gait, abnormal movements, and seizures. Sleep disorder is a common sign of non-severe and severe second-stage disease.

Acoziborole belongs to the family of benzoxaborole-6-carboxamides. It binds to and blocks the active site of the parasite enzyme named cleavage and polyadenylation specificity factor 3 (CPSF3). The mode of action differs from that of existing treatments. If authorised, would fulfil an unmet medical need in g-HAT patients by simplifying and reducing the medical burden of treatment - being a single dose, oral treatment that can be administered for both first and second stage disease, negating the need for lumbar puncture.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. of this document.

DNDi-OXA-02-HAT

The benefit-risk assessment relies primarily on a completed single pivotal phase 2/3 study (DNDi-OXA-02-HAT). This was a single-arm, open-label efficacy and safety study of a single oral dose of 960 mg acoziborole administered in a fasting state to participants ≥15 years old with parasitologically confirmed late-stage g-HAT. The study was carried out in DRC and Guinea.

Study eligibility required a suspicion of g-HAT disease based on clinical examination and rapid serological tests to be confirmed with parasitological testing and additionally lumbar puncture for staging, which is aligned with the case definition provided in current WHO guidance[18]. Outpatient follow up visits including parasitological tests on the blood ± lymph, as well as lumbar puncture for CSF

[18] WHO (2024). Guidelines for the treatment of human African trypanosomiasis. ISBN: 978-92-4-009603-5.

microscopy and parasitology, were thereafter performed at months 3, 6, 12, and 18 after acoziborole administration.

The primary study objective was to estimate the treatment success rate at 18 months of follow-up with acoziborole, administered as a single 960 mg oral dose to patients in the fasting state with late-stage g-HAT. The primary efficacy endpoint was Outcome (success or failure) at the 18 months visit according to the WHO 2013 criteria (adapted):

Treatment success:

- cure (participant alive, no evidence of parasites in any body fluids, and CSF WBC ≤20 cells/µL at M18 or later with non-haemorrhagic lumbar puncture), or probable cure (ie, participant without lumbar puncture at M18 but with CSF WBC ≤20 cells/µL at M12 or CSF WBC ≤50 cells/µL at M6, and no clinical signs or symptoms at M18);

***Treatment failure*:**

- relapse (evidence of trypanosomes in any body fluid within 18 months) or probable relapse (participant with a non-haemorrhagic lumbar puncture but CSF WBC >20 cells/µL at M18),
- death for any reason (within 18 months),
- use of rescue medication (within 18 months),
- loss to follow-up for any reason (within 18 months),
- refusal of all post-treatment lumbar puncture (within 18 months),
- in the absence of lumbar puncture at the M18 visit, an unfavourable outcome earlier than M18 (CSF WBC >50 cells/µL at M6 or >20 cells/µL at M12 or after M18), or signs and symptoms evoking a relapse at M18

The probability of confusing relapse/treatment failure of late-stage disease with reinfection during the 18-month follow-up period of the study is considered negligible as the estimated duration of the early stage of the disease, including following reinfection, is from 1.5 to 2 years.

Secondary efficacy endpoints included treatment success at 6 and 12 months in late-stage g-HAT, treatment success in early- and intermediate-stage g-HAT at all the same timepoints, and time to proven failure in late-stage g-HAT.

A total of 167 late-stage and 41 early- and intermediate-stage g-HAT cases were enrolled and treated within the study.

The late-stage g-HAT mITT analysis set was used for the primary analysis, which was provided descriptively as a point estimate and 95% Jeffreys CI. No formal hypothesis test was performed.

DNDi-OXA-04-HAT

A further completed, double-blind, placebo-controlled study (DNDi-OXA-04-HAT) in participants ≥15 years old with parasitologically non-confirmed g-HAT did not include efficacy variables but provided relevant additional safety and tolerability data. The study was executed in DRC and Guinea.
The participants underwent screening and were hospitalized for at least one day before treatment. The participants were randomized 3:1 to either receive acoziborole 960 mg (n=906) or placebo (n=300) orally at fasting state, and they remained in hospital for 5 days for observation after the administration. The study included follow-up at hospital one-month post-dose and contact with investigator two and three months after administration.

9.3. Favourable effects

The rate of treatment success amongst parasitologically confirmed late-stage g-HAT participants in the mITT analysis set at 18 months after study treatment (primary endpoint) was high at 159/167 (95.2%, [92.1–97.7%]). The result of the primary analysis is based on a near 100% rate of repeat lumbar puncture at M18 to provide a confirmed treatment success and failure rate at this timepoint.

The success rate at 6, 12 and 18 months in early- or intermediate-stage HAT patients was 100% (95% CI: 94.1; 100.0).

The total of 8 treatment failures at M18 in the primary analysis population of late-stage g-HET comprised 3 confirmed treatment failures at M18, 4 deaths and one loss to follow-up prior to primary EP. The 8 confirmed treatment failures all occurred in the most severe baseline severity subgroup E (positive CSF parasitology and CAF WBC ≥20 cells/µl), and all patients in less severe baseline categories met the criteria for treatment success at M18.

All pre-specified sensitivity analyses supported the result of the primary analysis. None of the cases of on-study offer death concrete evidence to support that death was the result of a lack of efficacy of acoziborole.

Secondary analyses were supportive of this conclusion, demonstrating that this high treatment success rate is in fact achieved by month 6. Additionally, all participants treated for early- and intermediate-stage g-HAT demonstrated treatment success by M6 (94.6%, [90.4–97.3%]) and sustained through M18.

9.3.1. Uncertainties and limitations about favourable effects

The Applicant provided confidence intervals (CIs) for the primary and secondary endpoints using the Clopper-Pearson exact method and compared them with Jeffreys 95% credible intervals from the Bayesian approach. Although the Clopper-Pearson 95% CI is a conservative method, it guarantees at least 95% coverage, but the CIs tend to be overly wide, particularly for small sample sizes. Both methods yielded consistent estimates of the CIs for the success rates with acoziborole and did not affect the interpretation of efficacy. However, as expected, Clopper-Pearson intervals were slightly wider, especially with small sample sizes, such as in early- and intermediate-stage cohorts.

Regarding the 3 participants who relapsed, it seems, from data provided, that no co-morbidities or co-medications were reported. However, all three patients had severe late-stage g-HAT at inclusion, with parasites detected in the CSF and WBC count >100 cells/µL, ranging from 455 to 971 cells/µL which is above the mean observed value for the participants with late-stage g HAT (398.8 ±438.4 cells/µL). Increase in CSF WBC was detected at Month 12 in all patients together with potentially g-HAT-related signs and symptoms. On one side, all the above might reasonably suggest the fact that patients with very severe late-stage g-HAT at baseline could be more susceptible to relapse after treatment, on the other side many participants with more severe baseline disease were successfully treated without relapse. However, a warning on risk of relapse after therapy, advising to instruct patients to contact the healthcare provider in case of occurrence of signs/symptoms of relapse has been added in section 4.4 of the SmPC, which is agreed.

The most credible theoretical mechanism of treatment emergent resistance is through amplification of gene copy number or point mutations that reduce binding of acoziborole to its target, TbCPSF3. There are no *in vivo* study data available and no standardised tests are yet developed to be used in the field. Based on the current state of knowledge, the uncertainties regarding resistance development are outweighed by the clinical benefit demonstrated. Resistance surveillance and the duty to report new emerging patterns that might impact the product's benefit-risk balance remain,

as always, the responsibility of the MAH in the post-marketing setting.

9.4. Unfavourable effects

The safety evaluation is mainly based on data from two phase II/III trials (DNDi-OXA-02-HAT, DNDi-OXA-04-HAT) where a total of 1114 participants received a single oral dose of 960 mg acoziborole at fasting state. Supportive safety data from three phase I trials evaluating different doses of acoziborole orally administered has also been presented.

In study -02 at least one TEAEs (after the date of administration of acoziborole up to study end) were reported in 74% of the participants. Nervous system disorders were reported in 31% in total (early/intermediate 34%; late 31%) and infections and infestations at a frequency of 31% (early/intermediate 20%; late 34%). The most reported PT in all stages of g-HAT were associated with the lumbar puncture: procedural pain (25%) and procedural headache (15%).

Other commonly reported PTs for the entire study population were headache (25%) pyrexia (15%) and malaria (14%). The PTs considered related to treatment by the investigator that were reported in ≥2 participants included pyrexia, asthenia, dyskinesia, tremor, headache, abdominal pain, decreased appetite. The following PTs considered related to treatment were reported once: chills, dizziness, nausea, vomiting and pruritus. These events are included as ADRs in the SmPC. All drug related events were mild or moderate at intensity and resolved.

Shortening of the QT interval corrected using Fridericia's formula (QTcF) was observed following a single dose of 960 mg. Shortening of QT-interval compared to baseline was observed in most participants in study -02. Across clinical studies, the observed QT interval shortening was most pronounced between 3 to 5 days following the dose. An early initial decrease was observed already at 4 hours (mean all participants -5,5 ms; SD 9,7) and 9 hours post dose (mean all participants -11,2 ms; SD 11,9). It should however be noted that the baseline-correction was suboptimal. Apart from this early initial decrease, the QT-interval had a second distinct trough at 72 hours following the dose (mean all participants: -11,1 ms; SD 10,8). The QT shortening remained at 240 h, which was the last ECG check in the study.

Given the long half-life of acoziborole (12 days), it can be expected that acoziborole induced QT-shortening remains longer than the observation period in this study. Shortening of QT-interval was also observed 5 days after dosing in the subset of participants in study -04 that underwent ECG investigation. The QT-interval was also studied in the healthy volunteer study DNDiOXA001 across several different dose levels. Study DNDiOXA001 included ECG measurements during follow-up, where the QT interval gradually returned to baseline within approximately 1 to 2 months. No dose-depending pattern could be identified. The molecular mechanism of this effect is not understood.

Acoziborole is a strong inducer of CYP3A4 but probably also many other enzymes and transporters including CYP2C enzymes, UGT-enzymes and Pgp. In addition, it is a strong CYP2D6 inhibitor. Given the long half-life of acoziborole the interaction risk may last for several months despite the single dose administration. This potentially complicates administration in clinical settings where patients may need acute or chronic treatment with interacting substances for other important conditions including, for example, HIV, tuberculosis and malaria.

Pregnancy was an exclusion criterion in the studies and there is very limited data on pregnancy in human. Acoziborole has a long duration, non-clinically it has been shown to cross the placenta and is excreted in millk in rats. Malformations are possibly present from the mid dose in rabbit, and the rabbit also show increased post-implantation losses and resorption increases already from the low dose (it can be noted that that clinical signs indicating more obvious maternal toxicity become manifest first

from the mid dose). Furthermore, the estimated rabbit-to-human exposure margins are <1x.

Based on the lactation exposure in rats, and also some degree of developmental growth retardation in lactation exposed rat offspring (in the rat PPND study), therefore acoziborole is not recommended at breastfeeding and should be avoided at pregnancy. Hormon contraception is also affected by the treatment of Acoziborole, and barrier methods are recommended to avoid pregnancy during the first 3 months after treatment.

Regarding fertility, it can be noted that while there were no adverse effects in a dedicated rat fertility (FEED) study, the general toxicity studies have shown male reproductive organ toxicity in rat and dog (including oligospermia in rats).

The target population includes paediatric patients (adolescents). The main difference between adults and adolescents that could lead to a difference in acoziborole PK is the expected lower body weight in adolescents than adults. A body weight cut-off of ≥ 40 kg is proposed for adolocents for the posology of 960 mg. Patients below 40 kg have numerically higher exposure (AUC and Cmax) compared to patients >40 kg which could translate to increased safety concerns in paediatric patients with low body weight, which could affect the B/R in this subpopulation. There are too few paediatric patients <40 kg in the clinical database to support that 960 mg has positive B/R in paediatric patients <40 kg. Furthermore, paediatric PopPK-based simulations indicate that a lower dose than 960 mg would be more appropriate in paediatric patients weighing <40 kg.

9.4.1. Uncertainties and limitations about unfavourable effects

In the clinical studies most of the participants experienced shorteing of QTcF-interval after administration of Acoziborole, which gradually returned to baseline within approximately 1 to 2 months. This is related to the long half-life of Acoziborole. Even though no events of arrythmia was reported in association with the observed shortening of QTcF-interval in the clinical studies, the clinical relevance of this observation is not fully clarified by the studies. The molecular mechanism of this effect is unknown and the effect was not dose dependent. Arrhythmia caused by shortening of QT interval is included as an important potential risk in the summary of safety concerns. Appropriate labelling describing this observation has been included in sections 4.4, 4.8 and 5.1 of the SmPC.

Pregnancy was an exclusion criterion in the studies and there is very limited data on exposure in pregnant women. Pharmacokinetic data in rats has demonstrated that Acoziborole crosses the placenta. It is therefore proposed in the product information to not use Acoziborole during pregnancy unless the woman requires immediate therapy and no other option is available.

There is no clinical data from breastfeeding. Non-clinically, acoziborole has a long duration, crosses the placenta and is excreted in milk in rats. Therefore, due to the likely risk of accumulation of acoziborole in breastfed children, it is suggested to not use Acoziborole during breastfeeding. Acoziborole has the potential to reduce hormonal contraceptive efficacy up to 3 months after administration, it is therefore proposed in the product information to use barrier contraception methods to avoid pregnancy during that period.

Acoziborole is a strong inducer of CYP3A4 and probably also many other enzymes and transporters including CYP2C enzymes, UGT-enzymes and Pgp. In addition, it is a strong CYP2D6 inhibitor. Given the long half-life (12 days) of acoziborole the interaction risk may last for several months despite the single dose administration. Appropriate labelling has been instituted.

9.5. Effects table

Table 70. Effects Table for Acoziborole Winthrop for treatment of g-HAT

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
PRIMARY EP Treatment success* @18 months, late-stage g-HAT, mITT analysis set	Acoziborole 960 mg PO 159/167 (95.2%) [91.2-97.7]%	N/A	**SoE:** Near 100% M18 lumbar puncture data (2/167 missing); essentially zero spontaneous cure in untreated infection. **Unc:** Single arm, open-label study; high rate of screening failures; high rate of protocol violations.	Study 02
Treatment success* @12 months, late-stage g-HAT, mITT analysis set	Acoziborole 960 mg PO 160/167 (95.8%) [91.9-98.1]%			
Treatment success* @6 months, late-stage g-HAT, mITT analysis set	Acoziborole 960 mg PO 158/167 (94.6%) [90.4-97.3]%		**SoE:** Essentially zero spontaneous cure in untreated infection. **Unc:** Single arm, open-label study; high rate of screening failures; high rate of protocol violations.	
Treatment success* @6, 12, 18 months, early- and intermediate stage g-HAT, mITT analysis set	Acoziborole 960 mg PO 41/41 (100%) [94.1-100.0]%			
Headache	Acoziborole 960 mg PO 32/208 (15,4%) up to D15 51/208 (24,5%) up to month 18	N/A	**SoE:** Reported up to D15 at hospitalization. Procedural headache reported separately. **Unc:** Single-arm study. Symptom can be related to g-HAT disease or lumbar puncture	Study 02
Asthenia	13/208 (6,3%) up to D15 18/208 (14,9%) up to month 18	N/A	**SoE:** Reported up to D15 at hospitalization **Unc:** Single-arm study. Symptom can be related to g-HAT disease	Study 02
Abdominal pain	7/208 (3,4%) 8/208 (3,8%) up to month 18	N/A	**SoE:** Reported up to D15 at hospitalization **Unc:** Single-arm study.	Study 02

Effect (short description)	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Pyrexia	7/208 (3,4%) up to D15 31/208 (14,9%) up to month 18	N/A	**SoE:** Reported up to D15 at hospitalization. **Unc:** Single-arm study. Can be associated to g-HAT, malaria or other infections.	Study 02

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; EP: endpoint; g-HAT: Gambiense HAT; HAT; human African trypanosomiasis; PO: orally; mITT: modified intention to treat.
*Defined according to WHO 2013 criteria with the adaptation that a death was always considered a failure.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The single pivotal study providing efficacy data was single-arm and open-label. Untreated late-stage g-HAT is considered an invariably chronic disease with near-zero spontaneous clearance of parasites. Thus, it is considered possible to infer absolute efficacy of the study treatment at M18 in late-stage HAT (i.e. over putative placebo) even in the absence of a placebo arm.

A single oral dose of acoziborole was shown to have comparable treatment success in late-stage g-HAT at 18 months to current recommended best available treatments (NECT, fexinidazole). The point estimate from study DNDi-OXA-02-HAT has better precision/ a narrower confidence interval versus some of the smaller historical studies, with a lower bound of the 95% CI in line with or above those reported for NECT and fexinidazole studies. This descriptive comparison supports the assumption of the roughly similar efficacy of acoziborole for the treatment of trypanosomiasis and its utility amongst existing therapeutic options.

The high observed success rate in study is comparable to that achieved in recent large Phase 3 and 4 studies of NECT (95-97%), which is a current standard of care effective in early-, intermediate-, and late-stage g-HAT. Considering the "worst case" effect estimate for acoziborole of 91.2% (at the lower margin of the 95% CI), any small true difference in efficacy versus NECT might be considered to be outweighed by the advantages in terms of clinical burden of administration.

The countries where the study was conducted, the DRC and Guinea, were the areas with the highest incidence of g-HAT reported cases at the time of study initiation, but the results are considered generalisable to other endemic countries where g-HAT elimination remains a public health problem.

Acoziborole offers a different mechanism of action to existing recommended treatments. Furthermore, the administration route (oral) and regimen (single dose) offer the potential to simplify and reduce the medical burden of treatment. Finally, having been demonstrated to be effective for both first and second stage disease, it negates the need for lumbar puncture prior to treatment.

The clinical safety database where a total of 1114 participants either seropositive or with parasitologically confirmed g-HAT have received acoziborole at 960 mg po is considered sufficient to identify the most commonly AEs. The long half-life and thereby the duration of the treatment is an important risk especially since acoziborole is both a strong inducer of CYP3A4 and many other enzymes and transporters (CYP2C, UGT and Pgp), and a strong CYP2D6 inhibitor which have an impact on many other medicines (including antimalarials and hormonal contraceptives) administered concomitantly.

A shortening of QT-interval was reported in almost all participants after administration of acoziborole, although no events of arrythmia related to the treatment was identified, the clinical relevance is unknown.

Acoziborole has (in preclinical data) been excreted in milk in rats and reproductive toxicity has been shown in preclinical studies. No or very limited data of use in pregnancy and breastfeeding in human is available.

It is reasonable to extrapolate the benefit-risk profile observed in the clinical studies to adolescents from 12 years of age provided that similar exposures are achieved, given the non-human pharmacological target, similarity of disease and expected similarity of response to treatment. Regarding body weight, a cut-off of 40 kg has been included in SmPC section 4.1 since the B/R of the proposed dose (960 mg) is too uncertain in paediatric patients <40 kg based on the totality of evidence.

9.6.2. Balance of benefits and risks

The high observed success rate in all stages of g-HAT disease, in addition to the reduced medical burden offered by a single oral dose treatment without the need for lumbar puncture, outweigh the most important risks of treatment (drug-drug interactions, shortening of QT-interval) as established from clinical studies.

9.7. Benefit-risk conclusions

9.7.1. At Day 120 CHMP conclusions

The benefit-risk balance of Acoziborole Winthrop is positive.