C O N F I D E N T I A L

CLINICAL STUDY PROTOCOL

Sponsor reference:	DNDi-OXA-07-HAT	**PhinC Development reference:**	PH21085
NMRR ID:	22-02194-VUI		

Study title:	A single centre open-label, non-randomised, three-treatment, two-period, pharmacokinetic drug interaction study of single oral dose of acoziborole with sequential co-administration of midazolam and dextromethorphan in healthy male participants
Drug name:	Acoziborole
Indication / purpose:	Human African Trypanosomiasis (HAT)
Drug development phase:	Phase I
Sponsor:	Drugs for Neglected Disease initiative (DNDi) Chemin Camille-Vidart, 15, 1202 Geneva, Switzerland Phone: +41 22 906 9230
Study center:	Clinical Research Ward (CRW) Clinical Trial Unit, Level 7, Hospital Ampang Jalan Mewah Utara, Pandan Mewah 68000 Ampang, Selangor, Malaysia Phone: + 603 4289 6558
Principal Investigator	Dr Sharon Ng Shi Min Clinical Research Ward (CRW) Clinical Trial Unit, Level 7, Hospital Ampang Jalan Mewah Utara, Pandan Mewah 68000 Ampang, Selangor, Malaysia
Protocol version:	Date of 2.0 edition: 05/01/2023, Amendment 01

PROTOCOL APPROVAL PAGE

Sponsor's representative

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I have read the protocol and will abide by it, will conduct study per ICH GCP and declaration of Helsinki as well as local guidelines.

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1 SYNOPSIS

Name of Sponsor/Company:

DNDi

Name of Finished Product:

Not applicable.

Name of Active Ingredient:

Acoziborole

Title of study:

A single centre, open-label, non-randomised, three-treatment, two-period, pharmacokinetic drug interaction study of single oral dose of acoziborole with sequential co-administration of midazolam and dextromethorphan in healthy male participants

Sponsor reference: DNDi-OXA-07-HAT **PhinC Development reference:** PH21085

Principal Investigator:

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Objectives:

Primary objective

- To assess the effect of single dose of acoziborole on pharmacokinetics (PK) parameters (C_{max}, AUC_{0-t}, and AUC_{0-24}) of midazolam as a probe substrate for CYP3A4 (induction) and of dextromethorphan as a probe substrate for CYP2D6 (inhibition).

Secondary objectives

- To evaluate the clinical and laboratory safety of acoziborole co-administered with midazolam and dextromethorphan as compared to administration of midazolam and dextromethorphan alone.
- To evaluate the other PK parameters of midazolam and dextromethorphan and PK parameters of their respective active metabolite, 1'-hydroxy-midazolam and dextrorphan (DXO), when co-administered with acoziborole.

Exploratory objective

- To evaluate the potential effect of acoziborole on plasma/serum levels of selected hormones (adrenal gland production and serum testosterone).

Endpoints:

Primary PK endpoints/parameters

- Midazolam C_{max}, AUC_{0-t}, and AUC_{0-24} of Period 1 and Period 2.
- Dextromethorphan C_{max}, AUC_{0-t}, and AUC_{0-24} of Period 1 and Period 2.

Secondary PK endpoints/parameters for acoziborole, midazolam and dextromethorphan

- Time to maximum observed plasma concentration (t_{max}) for midazolam and dextromethorphan.
- Apparent terminal elimination half-life ($t_{½}$) for midazolam and dextromethorphan.
- $AUC_{0-\infty}$ for midazolam and dextromethorphan.
- Acoziborole plasma concentrations.
- 1'-hydroxy-midazolam: C_{max}, t_{max}, AUC_{0-24}, AUC_{0-t}, $t_{½}$, $AUC_{0-\infty}$ for Period 1 and Period 2.
- DXO: C_{max}, t_{max}, AUC_{0-24}, AUC_{0-t}, $t_{½}$, $AUC_{0-\infty}$ for Period 1 and Period 2.

Secondary safety endpoints

- Frequency and cumulative incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) from time of first IMP administration (dextromethorphan on Day 1 in Period 1) to EoS visit.
- Vital signs for safety monitoring.
- 12-lead electrocardiogram (ECG) for safety monitoring purpose.
- Laboratory safety assessments from baseline to EoS visit.

Exploratory endpoint

- Plasma/serum concentration of selected hormones (adrenal gland production and serum testosterone), pre-dose as baseline, then on Day 12 (pre-dose), Day 14 and Day 21 following acoziborole administration.

Primary Endpoints Estimands:

Population: Healthy male participants aged 18 to 55 years old

Treatment condition:

- Acoziborole 960 mg (three tablets of 320 mg) for oral route in fasted condition
  Period 2: single oral administration on Day 12
- Midazolam 5 mg syrup in fasted condition
  Period 1: Single oral dose of 5 mg administered on Day 8
  Period 2: Single oral dose of 5 mg administered on Day 21
- Dextromethorphan 15 mg syrup in fasted condition
  Period 1: Single oral dose of 15 mg administered on Day 1
  Period 2: Single oral dose of 15 mg administered on Day 14

Endpoints: C_{max}, AUC_{0-t} and AUC_{0-24} for midazolam and dextromethorphan

Summary measures: Geometric mean ratios (GMR) between midazolam in absence or presence of acoziborole and dextromethorphan in absence or presence of acoziborole for C_{max}, AUC_{0-t} and AUC_{0-24} for midazolam and dextromethorphan.

Intercurrent events: Main anticipated intercurrent event is discontinuation of treatment. This event will be handled with the "while on treatment" strategy. Participants will be considered on treatment up to completion of the PK sampling profile of the last full dose received prior to the discontinuation.

Methodology/Study design:

This is a single centre, open-label, non-randomised, three-treatment, one-sequence, two successive periods study with at least 3-day washout between periods:

- Screening D-28 days
- Period 1 (9 days):
  - Admission on Day -1,
  - Single oral dose of dextromethorphan on Day 1,
  - Single oral dose of midazolam on Day 8,
  - Discharge on Day 9,
- Wash-out period (at least 3 days),
- Period 2 (11 days):
  - Admission on Day 11,
  - Single oral dose of acoziborole on Day 12,
  - Single oral dose of dextromethorphan on Day 14,
  - Single oral dose of midazolam on Day 21,
  - Discharge on Day 22,
- Follow-up between 7 and 10 days after last dose of midazolam in Period 2.

Number of participants:

Planned: 20 healthy male participants aged 18 to 55 years old to have 16 evaluable participants.

Diagnosis and main criteria for inclusion:

The study will be carried out in healthy male participants, aged 18 to 55 (inclusive) years old. BMI will be between 18 and 30 kg/m² (inclusive). Participants will be non-smokers for at least 3 months prior to the first dose.

Study duration:

The participation of each participant will last approximately 8 weeks and includes:

- A selection period of up to 28 days before dosing,
- Period 1 (hospitalisation for 9 days): Participants will come to the clinic a day before the first dosing until 1 day after the first midazolam administration,
- Wash-out period: at least 3 days,
- Period 2 (hospitalisation for 11 days): Participants will come to the clinic a day before the acoziborole dosing until 1 day after the last midazolam administration.

Participants will come back for a short visit to the study centre for specimen collection and safety follow-up, between 7 and 10 days after the last drug administration.

Dosage regimen:

Each participant will receive the following treatments:

- Acoziborole 960 mg (three tablets of 320 mg) for oral route in fasted condition
  - Period 2: single oral administration on Day 12
- Midazolam 5 mg syrup in fasted condition
  - Period 1: Single oral dose of 5 mg administered on Day 8
  - Period 2: Single oral dose of 5 mg administered on Day 21
- Dextromethorphan 15 mg syrup in fasted condition
  - Period 1: Single oral dose of 15 mg administered on Day 1
  - Period 2: Single oral dose of 15 mg administered on Day 14

Hospitalisation:

Participants will be admitted into the unit:

Period 1: On the day before the first dose of dextromethorphan until 24 h post-first administration of midazolam (9 days).

Period 2: On the day before single administration of acoziborole until 24 h post-last administration of midazolam (11 days).

Criteria for evaluation:

Efficacy/PD:

Not applicable.

PK:

- For midazolam and its active metabolite (1'-hydroxy-midazolam), blood samples will be collected for concentration measurements at the following times: baseline, 15 min, 30 min, 1.0 h, 1 h 30 min, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0, 12.0 and 24.0 h post-dosing for Period 1 and Period 2.
- For dextromethorphan and its active metabolite (dextrorphan), blood samples will be collected for concentration measurements at the following times: baseline, 30 min, 1.0, 2.0 ,3.0 ,4.0 ,6.0 ,7.0 ,8.0 ,12.0, 24.0, 36.0, 48.0 and 72.0 h post-dosing for Period 1 and Period 2.
- For acoziborole, blood samples will be collected for concentration measurements at the following times: baseline on Day 12 (before acoziborole administration), then on Day 14 (before dextromethorphan administration), Day 18 and Day 21 (before administration of midazolam) in Period 2.

For midazolam and dextromethorphan and their respective metabolites, the following PK parameters will be determined: C_{max}, t_{max}, AUC_{0-24}, AUC_{0-t}, $t_{½}$, $AUC_{0-\infty}$.

For acoziborole only plasma concentrations will be presented.

Hormone level:

Blood samples will be 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.

For each hormone, values obtained at pre-dose (*i.e*. on Day 2, Day 3 and Day 4) will be pooled and mean value will be used as baseline to decrease the variability.

Safety:

Safety measurements (12-lead ECG, vital signs, blood chemistry and haematology) will be performed before, during the study and at end of study and AEs will be monitored throughout the study.

Statistical methods:

Efficacy/PD:
Not applicable.

PK:

- For each analyte:
  - Concentrations will be summarised by treatment and time points.
  - The derived PK parameters will be listed by participant and summarised by treatment.
- For midazolam and dextromethorphan separately, the log transformed PK parameters will be analysed using a mixed ANOVA model including fixed effect for treatment (*i.e*. with or without acoziborole) and the participant as random effect. The GMR (midazolam or dextromethorphan with/without acoziborole) and their 95% CI will be computed by back transforming the differences between treatments and their 95% CI obtained from the ANOVA in log scale.

Hormone level:

- Hormone levels will be summarised by time points.

Safety:

- All safety parameters (ECG, vital signs, AEs, laboratory tests, etc.) will be summarised by treatment and time point (where appropriate).
- Changes in physical examination, vital signs (BP, pulse rate, respiratory rate and body temperature), ECG and clinical laboratory tests (clinical chemistry, haematology, and urinalysis).

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

°C	Degree Celsius
µL	Microlitre
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ALQ	Above the limit of quantification
AMP	Amphetamines
ANOVA	Analysis of variance
ASAT	Aspartate aminotransferase
AUC	Area under the curve
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BZO	Benzodiazepines
Ca^{2+}	Calcium
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cl^-	Chloride
C_{max}	Maximum concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
CPSF3	Cleavage and polyadenylation specificity factor 3
CRW	Clinical Research Ward
CSF	Cerebrospinal fluid
CSR	Clinical study report
CV/CV%	Coefficient of variation
CYP	Cytochrome P450
D	Day
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DHEA-S	Dehydroepiandrosterone-sulphate
DMP	Data management plan
DNDi	Drugs for Neglected Disease initiative
DXM	Dextromethorphan
DXO	Dextrorphan
e-CRF	Electronic case report form
e.g.	*Exempli gratia* (for example)
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimate glomerular filtration rate
EMA	European Medicines Agency
EoS	End of study
FDA	Food and Drug Administration
g-HAT	Trypanosoma brucei gambiense

GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyltranspeptidase
GM	Geometric mean
GMR	Geometric mean ratio
h	Hour(s)
HAT	Human African Trypanosomiasis
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
i.e.	*Id est* (that is)
i.v.	intravenous
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INN	International non-proprietary name
ITT	Intent-to-treat
K^+	Potassium
k_e	Terminal plasma elimination rate-constant
KET	Ketamine
kg	Kilogram(s)
L	litre
LC-MS/MS	Liquid chromatography mass spectrometry tandem
LLOQ	Lower limit of quantification
ln	Neperian logarithm
log	Decimal logarithm
LOQ	Limit of quantification
m	Meter
Max	Maximum
MCH	Mean corpuscular haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MET	Methamphetamine
mg	Milligram(s)
MGCP	Malaysian Good Clinical Practice
min	Minute(s)
Min	Minimum
mL	Millilitre(s)
mm	Millimetre(s)
mmHg	Millimetre mercury
MOP	Morphine
mRNA	Messenger ribonucleic acid

ms/msec	Millisecond(s)
mV	Millivolt(s)
N	Number of observation
Na^+	Sodium
NECT	Nifurtimox-eflornithine combination therapy
ng	Nanogram(s)
NMRR	National Medical Research Register
NOAEL	No observed adverse effect level
NPRA	National Pharmaceutical Regulatory Agency
NR	Not reported
OTC	Over-the-counter
PB-PK	Physiologically based pharmacokinetics
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PR	Distance in ms between the P and the R wave
PT	Preferred term
QRS	Distance in ms between the Q and the S wave
QT	QT interval
QTc	Corrected QT interval
QTcF	Fridericia's correction QT interval
r-HAT	Trypanosoma brucei rhodesiense
RBC	Red blood cells
RDW	Red cell distribution width
SAE	Serious adverse event
SAC	Serum aldosterone concentration
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SMM	Study medical manager
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
T.b.	Trypanosoma brucei
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
THC	Tetrahydrocannabinol
TK	Toxicokinetics
t_{max}	Time of occurrence of maximum concentration
VPN	Virtual private network
vs.	*versus*
WBC	White blood cells
WHODRUG	World Health Organization Drug Dictionary
WMA	World Medical Association

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4 INTRODUCTION

4.1 Background

Human African trypanosomiasis (HAT, also called sleeping sickness) is a life-threatening disease transmitted by tsetse flies and caused by a single celled extracellular parasite that lives free in the bloodstream and other body fluids, including lymph and cerebrospinal fluid (CSF). There are many species, however, only those of the *Trypanosoma brucei (T. b.)* species are known to infect humans. Two subspecies are pathogenic for humans:

- *T. b. gambiense* is endemic in West and Central Africa and causes over 95% of current cases (g-HAT). It progresses at a more indolent pace than that of T. b. rhodesiense,
- *T. b. rhodesiense* is endemic in East and Southern Africa and accounts for 5% of cases (r-HAT). It causes an acute, rapidly progressive infection.

***Epidemiology*:** HAT is considered endemic in 36 countries, of which 24 are endemic for *T. b. gambiense* (g-HAT). In 2012, the number of new T. b. gambiense cases reported to World Health Organization (WHO) were fewer than 8,000 (7,106), decreased to 876 cases reported in 2019 and further decline to 565 in 2020 (~70% of cases in Democratic Republic of the Congo). The number of yearly reported cases constantly decreases. However, care should be taken, and the cases reported may underestimate the real status of the disease due to the limited effective health surveillance in some g-HAT endemic regions.

Clinical stages: g-HAT occurs in two clinical stages. During the early haemolymphatic stage (Stage 1), trypanosomes reside in the blood and lymphatic system, and clinical signs and symptoms are mild and non-specific.

In the following late stage (meningo-encephalitic, Stage 2) the parasites invade the central nervous system (CNS) and patients exhibit the characteristic neurological and psychiatric manifestations of disorientation, abnormal gait, abnormal movements, increasing sleep disturbances and eventually coma and death[(1)].

Diagnosis: HAT is diagnosed after a clinical suspicion, serological tests, which should be confirmed by lumbar puncture followed by CSF examination. Stage is determined by the number of white blood cells (WBC) and the presence of trypanosomes in CSF examination.

Treatments available: Few treatment options are currently available for either disease stage: in particular, available drugs for Stage 2 were so far limited to the old and toxic melarsoprol, and to the less toxic but difficult to manage eflornithine, which requires 4 intravenous (i.v.) infusions per day for 14 days.

A recently developed combination of 10-day oral nifurtimox plus 7-day eflornithine, 2 i.v. infusions per day (Nifurtimox-eflornithine combination therapy (NECT)) was shown to provide similar cure rate as a full regimen of eflornithine[(2)], with an obvious practical advantage in terms of reduction of treatment duration and ease of administration. Though NECT became the most used treatment for late-stage disease since 2010, the treatment is still far from ideal in the environment in which g-HAT patients leave.

WHO recommendations: WHO recommended (May 2019) fexinidazole as first line of treatment for g-HAT in patients aged ≥ 6 years and body weight ≥ 20 kg presenting without clinical features consistent with severe meningo-encephalitic g-HAT or presenting with < 100 WBC/µL in CSF. Pentamidine is the first-choice treatment in patients aged < 6 years or body weight < 20 kg with ≤ 5 WBC/µL CSF and no trypanosomes in the CSF. NECT is the first-choice treatment in patients with clinical features suggestive of with severe meningo-encephalitic HAT with ≥ 100 WBC/µL CSF or if no CSF data WBC is available. It is also the first-choice treatment in patients aged < 6 years or body weight < 20 kg with > 5 WBC/µL or trypanosomes in the CSF.

The difficulty of diagnosis, stage determination, and increasing number of treatment failures pose additional clinical challenges. An urgent need exists to develop novel oral drugs for the treatment of both stages of this fatal disease. Single dose treatment offers an additional advantage over existing options as it ensures full compliance, does not require skilled health staff for administration and, if devoid of need for monitoring and well tolerated, is thermostable and easy to administer and safe in non-specialised centres, in extremely remote areas or in conflict zones, representing therefore an additional tool to meet WHO's goals to contain the transmission by 2030.

A single-dose safe and effective treatment for patients with Stage 1 and Stage 2 g-HAT without the need for staging lumbar puncture would also facilitate attainment of the WHO goal of sustained elimination by 2030.

4.2 Clinical pharmacokinetics

Acoziborole is an oxaborole-6 carboxamide, formulated for oral administration. Acoziborole binds and blocks the active site of cleavage and polyadenylation specificity factor 3 (CPSF3), a metallo-β-lactamase that processes messenger ribonucleic acid (mRNA) and facilitates gene expression. This action results in inhibition of maturation of mRNA of the parasite and not the host CPSF3[(3)]. Acoziborole is active *in vitro* against both *T. b. rhodesiense* and *T. b. gambiense* parasites. Preclinical pharmacokinetic (PK) studies have indicated that acoziborole is well absorbed by the oral route, highly bound to proteins and widely distributed throughout the body. The compound crosses the blood brain barrier. In all animal species investigated, acoziborole is rapidly metabolized through oxidation, resulting in the formation of at least one non-active metabolite (SCYX-3109, oxidative deboronation)[(4)]. It should be noted that in human situation seems different with circulating levels of SCYX-3109 being extremely low and acoziborole being mainly excreted by the liver unchanged.

Preclinical studies: Acoziborole did not affect CNS, cardiovascular or respiratory functions, or intestinal transit in preclinical studies. Toxicological studies, including safety pharmacology and 4-week repeated-dose toxicity (with toxicokinetics (TK)) in the rat and dog, have shown that acoziborole is well tolerated up to 40 mg/kg/day in rat, with no major toxicities identified. In both species, 15 mg/kg/day was considered as the no observed adverse effect level (NOAEL) in 4-week repeated-dose studies.

Complementary toxicity studies to the previous 28-day pivotal ones have been conducted to fully cover the length of time patients will be exposed. In these GLP studies, rat and dogs were treated for 13 weeks followed by a 6-week recovery period. Administrated doses were 30, 15 and 5 mg/kg in the rat every day, and 20, 15 and 5 mg/kg every other day in the dog. Following administration of acoziborole for 13 weeks, the NOAEL was 5 mg/kg and 20 mg/kg in rats and dogs, respectively.

Phase 1 studies: In the Single Ascending Dose Phase 1 study (DNDi-OXA-01-HAT) in healthy participants, 128 participants were enrolled, of which 102 received acoziborole by oral route at doses from 20 to 1200 mg. The study drug was well tolerated at highest dose of 1200 mg and showed a good safety profile with no dose-related adverse events (AEs). PK results showed that acoziborole was quite rapidly absorbed and that plasma levels remained steady for at least 96 hours. The half-life ($t_{1/2}$) was calculated to be around 360 hours. Inter-subject variability at around 20%. All TEAEs were mild or moderate. No deaths occurred, and only 1 SAE ("asymptomatic hyperthyroidism") was reported "after a single oral dose of 240 mg acoziborole that was mild in severity, transient and resolved spontaneously in 24 hours. It was assessed as possibly related to the treatment. No other case of hyperthyroidism have been reported in other clinical trial, this is an isolated case.

DNDi conducted then a multicentre, open-label, prospective Phase II/III study to assess the efficacy and safety study of single dose of 960 mg acoziborole in 208 patients with HAT Stage 1 and Stage 2 due to *T. b. gambiense*. The efficacy results from 167/208 late Stage 2 patients showed 95.6% success at 18 months (intent-to-treat (ITT)). Acoziborole showed high efficacy in any stage of HAT, which was comparable to that

of the reference treatment NECT (see Section 4.1) used as a yardstick. The safety data collected during this study did not result in any significant drug-related safety signals. Based on these findings, the benefit-risk balance for treating g-HAT patients, regardless of disease stage, with a single oral dose of acoziborole appears favourable.

A Phase I study was conducted to assess the mass balance recovery and PK of acoziborole, and metabolite profiling and identification following administration of an oral dose of 960 mg of [^{14}C]-acoziborole to 6 healthy participants. Acoziborole was well tolerated with no withdrawals due to AEs in the study. Four (4) months after administration, all 6 participants reached the plasma acoziborole and total radioactivity lower limit of quantification (LLOQ). That study demonstrated that in human, acoziborole is weakly metabolized and undergoes mainly liver/biliary clearance and excretion unchanged in faeces. In faeces, over 10 days, acoziborole represents 66% of the radioactivity excreted, whereas SCYX-3109 represents 24% of the radioactivity and 2 oxidative metabolites represent 4.6% of the radioactivity. Urine is a minor elimination pathway. In plasma, the main circulating moiety is acoziborole, which represents 95% of total radioactivity.

4.3 Risk assessment

The benefit-risk balance of acoziborole in g-HAT in the on-going and new studies remains positive and the risks remain acceptable for testing in healthy participants.

Dextromethorphan (DXM; d-methorphan) is a non-narcotic synthetic analog of codeine (widely used as an antitussive agent in over-the-counter (OTC) treatment of cough and cold medications, it is considered safe and effective when taken at oral therapeutic doses (30 mg every 6 to 8 h)). DXM has been adopted as a metabolic probe of CYP2D6 in humans

Midazolam, a benzodiazepine sedative-hypnotic agent, is metabolized by CYP3A and accepted as a probe for CYP3A in humans. When used with vigilance, appropriate patient monitoring, and slow, careful titration to desired effect, midazolam is useful and safe medication for both inpatients and outpatients. Oral midazolam taken at a dose range of 7.5 – 15 mg is indicated in healthy adults for the short-term treatment of insomnia and anxiety, as well as for sedation in premedication before surgical or diagnostic procedures.

5 RATIONALE

5.1 Rationale for administration of single dose of acoziborole and of the 2 cytochrome P450 probes

The rationale for the single dose design for acoziborole is that in the Phase I studies in healthy participants, a long $t_{1/2}$ of 360 hours was observed in single ascending dose study (DNDi-OXA-01-HAT study). As a consequence, a single dose of acoziborole was used in Phase 3, resulting in good (over 95%) efficacy. This single dose is targeted for submission to Health Authorities for Market Authorization.

In vitro, a number of interactions between acoziborole and metabolizing enzymes and transporters were identified. The most pronounced were with cytochrome P450 2D6 (CYP2D6) (time-dependent inhibition), with CYP3A4 (induction) and with CYP2C8 (induction).

An *in silico* physiologically based PK (PB-PK) model was developed within the simCYP software and qualified for acoziborole. This study suggested minimal to weak interaction with the transporters OAT-3, OCT 2/MATEs, OATP1B1 and with CYP1A2, CYP2B6 and CYP2C9; moderate interactions with CYP2C8 and CYP2C19 substrates; strong interactions with sensitive index substrates of CYP2D6 and CYP3A4.

To validate these PB-PK model results, it was decided to evaluate clinically the potential impact of acoziborole on plasma exposure of two different sensitive CYP substrates, dextromethorphan (DXM) for CYP2D6 and midazolam for CYP3A4. For dextromethorphan, the strong CYP2D6 inhibition detected in the PB-PK study

(geometric mean ratio (GMR) of AUC in absence and presence of acoziborole of 8.34) suggests a high potential of acoziborole to significantly increase dextromethorphan plasma concentrations. Also, the PB-PK study has suggested a strong induction of CYP3A4, resulting in midazolam area under the concentration curve (AUC) in the presence of acoziborole being 0.06 times the one in absence of acoziborole.

Dextromethorphan (DXM; d-methorphan) is a non-narcotic synthetic analog of codeine (widely used as an antitussive agent in over-the counter (OTC) treatment of cough and cold medications, it is considered safe and effective when taken at therapeutic doses (30 mg every 6 to 8 h)). DXM is primarily rapidly and extensively O-demethylated by CYP2D6 to dextrorphan (DXO), its major, active metabolite. DXM has been adopted as a metabolic probe of CYP2D6 in humans[5].

Dextromethorphan is well absorbed orally and following oral administration. Following a 30-mg oral dose of DXM in healthy participants (none being identified as poor metabolizer), mean maximal plasma concentrations of about 1.3 ng/mL were observed at 2.0 h post dose. Maximal plasma concentrations decreased with a mean $t_{1/2}$ of 8 h. The corresponding maximal plasma concentration of the dextromethorphan was 490 ng/mL observed at 2.0 h. The mean $t_{1/2}$ of the metabolite was 6 h[6]. A single 15 mg oral dose that is the dose usually used in interaction studies will allow a good estimation of PK parameters. Dextromethorphan will be given on Day 14 in Period 2 *i.e*. 2 days following oral administration of acoziborole. The SimCYP simulations suggest that the best compromise to maximize the CYP2D6 inhibition and minimize the CYP3A4 induction is when DXM is given 24 to 60 h after acoziborole administration.

Midazolam, a benzodiazepine sedative-hypnotic agent, is metabolized by CYP3A and accepted as a probe for CYP3A in humans[5].

A single 5 mg oral dose of midazolam is expected to allow a good estimation of PK parameters. Indeed, following a 5 mg oral dose in healthy participants, mean maximal plasma concentrations (C_{max}) was reported to be about 28 ng/mL at 0.5 h post-dose. Maximal plasma concentrations decreased then rapidly with a mean $t_{1/2}$ of 5 h. The corresponding maximal plasma concentration of the metabolite 1-hydoxy-midazolam was 15.1 ng/mL observed at 0.5 h. The mean $t_{1/2}$ of the metabolite was 5 h[7]. Based on the PB-PK simulations, the interaction between acoziborole and midazolam should be maximal around Day 8 (due to the activity CYP3A4) and sustained for several weeks after. Thus, midazolam will be given on Day 21 in Period 2 *i.e*. 9 days following oral single administration of acoziborole.

5.2 Rationale for hormones exploration

In 13-week toxicology study in rats and dogs with acoziborole, vacuolation of cortical cells in the adrenal gland (with minimal to moderate severity) in the mid and high dose male groups (15 mg/kg/day and 30 mg/kg/day, respectively) was noted on study Day 92. Spermatic granulomas in the epididymis of rat males treated with mid and high dose were also reported at low incidence on Day 92. The changes in the adrenal gland observed only in male rats and epididymis were not reversible as these findings were still noted to be present (with minimal to mild severity) at the end of a 6-week recovery. In total, throughout the 4 groups, changes were observed in none of the 5 animals in Group 1, in 2 out of 4 animals in Group 2, in 1 out of 5 animals in Group 3 and in 2 out of 5 animals in Group 4. Electron microscopy revealed that the vacuoles in the adrenal gland were consistent with cytoplasmic lipid accumulation. To complete the preclinical data of acoziborole generated in the above study, the exploration of possible effects of acoziborole after dosing at the therapeutic dose in human on a panel of adrenal hormones may be informative.

Therefore, in the drug-drug interaction (DDI) clinical study, the plasma and serum levels of the following will be determined:

Adrenal cortex production:

- Fasciculata zone production: serum cortisol (taking the nocturnal cycle into account).

- Reticularis zone production: serum dehydroepiandrosterone-sulphate (DHEA-S), serum androstenedione (both adrenal and testis production).
- The concentration of plasma adrenocorticotropic hormone (ACTH) will evaluate the pituitary gland.
- Glomerulosa zone production : serum aldosterone concentration (SAC).

Evaluation of serum testosterone levels was requested by the European Medicines Agency (EMA) due to findings of spermatic granulomas in the epididymis, yielding further relevant information.

6 STUDY OBJECTIVES AND ENDPOINTS/ESTIMANDS

6.1 Study objectives

6.1.1 Primary objective

To assess the effect of single dose of acoziborole on PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-24}) of midazolam as a probe substrate for CYP3A4 (induction) and of dextromethorphan as a probe substrate for CYP2D6 (inhibition).

6.1.2 Secondary objectives

- To evaluate the clinical and laboratory safety of acoziborole co-administered with midazolam and dextromethorphan as compared to administration of midazolam and dextromethorphan alone.
- To evaluate the other PK parameters of midazolam and dextromethorphan and PK parameters of their respective active metabolite, 1'-hydroxy-midazolam and DXO, when co-administered with acoziborole.

6.1.3 Exploratory objective

To evaluate the potential effect of acoziborole on plasma/serum levels of selected hormones (adrenal gland production and serum testosterone).

6.2 Study endpoints

6.2.1 Primary endpoints

- Midazolam maximum concentration (C_{max}), area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration (AUC_{0-t}), and area under the concentration-time curve from time zero (pre-dose) to 24 h after administration (AUC_{0-24}) of Period 1 and Period 2.
- Dextromethorphan C_{max}, AUC_{0-t}, and AUC_{0-24} of Period 1 and Period 2.

6.2.2 Secondary endpoints

6.2.2.1 PK endpoints

Secondary PK endpoints/parameters for acoziborole, midazolam and dextromethorphan

- Time to maximum observed plasma concentration (t_{max}) for midazolam and dextromethorphan.
- Apparent terminal elimination $t_{1/2}$ for midazolam and dextromethorphan.
- Area under the concentration-time curve from time zero (pre-dose) to infinity ($AUC_{0-\infty}$) for midazolam and dextromethorphan.
- Acoziborole plasma concentrations.

- 1'-hydroxy-midazolam: C_{max}, t_{max}, AUC_{0-24}, AUC_{0-t}, $t_{½}$, $AUC_{0-\infty}$ for Period 1 and Period 2.
- DXO: C_{max}, t_{max}, AUC_{0-24}, AUC_{0-t}, $t_{½}$, $AUC_{0-\infty}$ for Period 1 and Period 2.

6.2.2.2 Safety endpoints

- Frequency and cumulative incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) from time of first IMP administration (dextromethorphan on Day 1 in Period 1) to EoS visit.
- Vital signs for safety monitoring.
- 12-lead electrocardiogram (ECG) for safety monitoring purpose.
- Laboratory safety assessments from baseline to EoS.

6.2.3 Exploratory endpoint

Plasma/serum concentration of selected hormones (adrenal gland production and serum testosterone), 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.

6.3 Estimands

The estimands for primary PK endpoints are:

Population: Healthy male participants aged 18 to 55 years old

Treatment condition:

- Acoziborole 960 mg (three tablets of 320 mg) for oral route in fasted condition
  - Period 2: single oral administration on Day 12
- Midazolam 5 mg syrup in fasted condition
  - Period 1: Single oral dose of 5 mg administered on Day 8
  - Period 2: Single oral dose of 5 mg administered on Day 21
- Dextromethorphan 15 mg syrup in fasted condition
  - Period 1: Single oral dose of 15 mg administered on Day 1
  - Period 2: Single oral dose of 15 mg administered on Day 14

Endpoints: C_{max}, AUC_{0-t} and AUC_{0-24} for midazolam and dextromethorphan

Summary measures: GMRs between midazolam in absence or presence of acoziborole and dextromethorphan in absence or presence of acoziborole for C_{max}, AUC_{0-t}, and AUC_{0-24} for midazolam and dextromethorphan.

Intercurrent events: Main anticipated intercurrent events is discontinuation of treatment. This event will be handled with the "while on treatment" strategy. Participants will be considered on treatment up to completion of the PK sampling profile of the last full dose received prior to the discontinuation.

7 STYDY DESIGN

7.1 Overall study design

This is a Phase I, single centre, open-label, non-randomised, three-treatment, one-sequence, two successive periods study with at least 3-day washout between periods.

A total of 20 healthy male participants aged 18 to 55 years old will be enrolled to have 16 evaluable participants.

On Period 1 (from Day -1 to Day 9), participants will receive:

- A single oral dose of dextromethorphan on Day 1,
- A single oral dose of midazolam on Day 8.

On Period 2 (from Day 11 to Day 22), participants will receive:

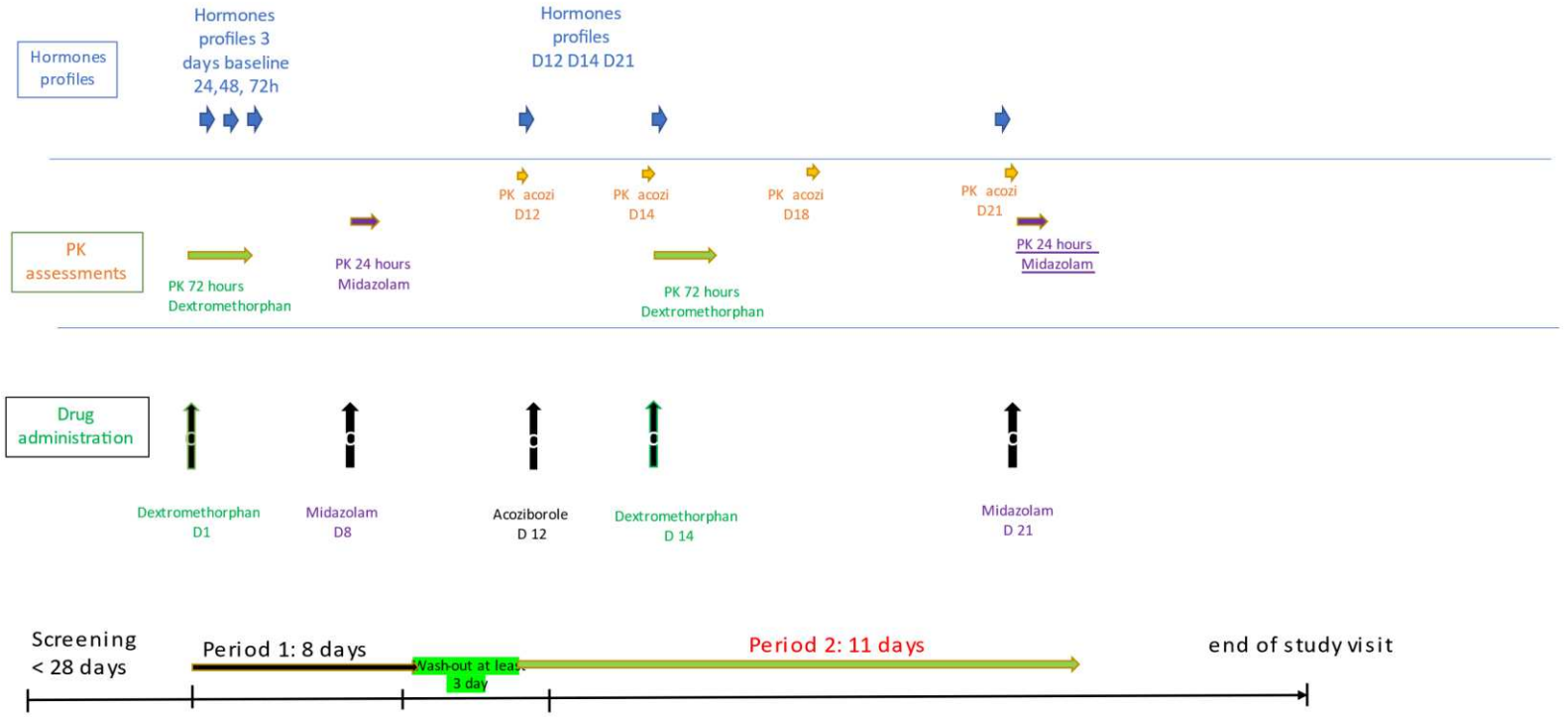
- A single oral dose of acoziborole on Day 12,
- A single oral dose of dextromethorphan on Day 14,
- A single oral dose of midazolam on Day 21.

Overall study design is presented in Figure 1.

The study duration will be approximately 8 weeks and will include:

- Screening period of up to 28 days before the first study drug administration,
- Period 1 (9 days) with a hospitalisation period from the day before the first dose of dextromethorphan (*i.e*. Day –1) until 24 h after the first dose of midazolam (*i.e*. Day 9 morning),
- Wash-out period: 3 days,
- Period 2 (11 days) with a hospitalisation period from the day before the single administration of acoziborole (*i.e*. Day 11) until 24 h after the last dose of midazolam (*i.e*. Day 22 morning)
- End of study (EoS) visit between 7 and 10 days after last dose of midazolam on Period 2 (see Table 1 in Section 7.3).

Figure 1 DNDi-OXA-07-HAT overall study design



7.2 Rationale for study design

An *in silico* PB-PK model was developed within the simCYP software and qualified for acoziborole. This study suggested strong interactions with sensitive index substrates of CYP2D6 and CYP3A4.To validate these PB-PK model results, an open-label, non-randomised, three-treatment, one-sequence, two successive periods study with at least 3-day washout between periods was chosen to evaluate clinically the potential impact of acoziborole on plasma exposure of two different sensitive CYP substrates, DXM for CYP2D6 and midazolam for CYP3A4.

Acoziborole will be administered as a single dose, due to the long $t_{1/2}$ of 360 h in healthy participants.

The SimCYP simulations showed that the best compromise to maximize the CYP2D6 inhibition and minimize the CYP3A4 induction is when DXM is given 24 to 60 h after acoziborole administration. Therefore, dextromethorphan will be given on Day 1 (in Period 1, without acoziborole) and on Day 14 in Period 2 *i.e.* 2 days following oral administration of acoziborole.

Based on the PB-PK simulations, the interaction between acoziborole and midazolam should be maximal around Day 8 (due to the activity CYP3A4) following acoziborole administration and sustained for several weeks after. Thus, midazolam will be 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.

7.3 Study plan

Study plan is presented in Table 1.

Table 1 Study plan

Study day	Screening	Period 1										Wash out	Period 2												EoS	Comments
	D-28 to D-1	D-1	D1	D2 (24h)	D3 (48h)	D4 (72h)	D5	D6	D7	D8	D9		D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	**D28 to D31**	**EoS between 7 and 10 days after last dose of midazolam on Period 2**
Informed consent	X																									
Admission		X											X													
Discharge											X													X		
Medical and Surgical history	X	X																								***The recorded medical history will be updated if necessary, on admission to Treatment Period 1 and any time if new information becomes available.***
Vein assessment	X																									
Demographic data	X																									***Sex, race, age, height and body weight.***
Prior medications		X																								
Concomitant medications		←																						→		
Inclusion/Exclusion criteria	X	X																								
Hepatitis B &C/HIV serology	X																									
COVID-19 rapid Testing	X	X											X													

Study day	Screening	Period 1											Period 2												EoS	Comments
	D-28 to D-1	D-1	D1	D2 (24h)	D3 (48h)	D4 (72h)	D5	D6	D7	D8	D9		D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	**D28 to D31**	**EoS between 7 and 10 days after last dose of midazolam on Period 2**
Urine drug screen	X	X											X													
Alcohol Breath test	X	X											X													
Cotinine test	X																									
Genotyping	X																									
IMP administration																										
Acoziborole														X												
Midazolam										X													X			
Dextromethorphan			X													X										
Safety assessment																										
Physical examination	X	X									X		X											X	X	***should include general appearance, skin, head and neck, eyes, ears, nose, throat, lymph node palpation, lungs, heart, chest, abdomen, neurological function***
Complaint directed physical			←																					→		

Study day	Screening	Period 1										Period 2												EoS	Comments
	D-28 to D-1	D-1	D1	D2 (24h)	D3 (48h)	D4 (72h)	D5	D6	D7	D8	D9	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	**D28 to D31**	**EoS between 7 and 10 days after last dose of midazolam on Period 2**
examination																									
Compliance assessment		X										X													
Height, body weight and BMI	X																							X	***Body height is recorded only at screening***
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X									X	X											X	X	
Adverse events	←	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———		***Before first administration, collection of events from ICF signature***
Haematology, biochemistry, urinalysis	X	X										X											X	X	***See Table 4 laboratory parameters***
Hormone level				X	X	X							X		X							X			

Study day	Screening	Period 1										Period 2												EoS	Comments
	D-28 to D-1	D-1	D1	D2 (24h)	D3 (48h)	D4 (72h)	D5	D6	D7	D8	D9	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	**D28 to D31**	**EoS between 7 and 10 days after last dose of midazolam on Period 2**
Pharmacokinetics																									
Acoziborole PK samples													X		X				X			X			***Day 12 (before acoziborole administration), then on Day 14 (before DXM administration), Day 18 and Day 21 (before administration of midazolam) in Period 2***
Midazolam and metabolite PK samples										X	x											X	X		***Baseline, 15 min, 30 min, 1 h, 1 h 30 min,, 2, 3, 4, 6, 7, 8, 12, 24 h post-dosing for Period 1 and Period 2***
Dextromethorphan and metabolite PK samples			X	X	X	X									X	X	X	X							***Baseline, 30 min, 1, 2, 3, 4, 6, 7, 8, 12, 24, 36, 48 and 72 h post-dosing for Period 1 and Period 2***

8 STUDY POPULATION

Participants will be healthy male volunteers recruited by Clinical Research Ward (CRW), Ampang, Malaysia. In accordance with the protocol full schedule and with regulation and international standards.

Participants will be screened for the study, according to the criteria for inclusion and exclusion, up to 28 days before first dosing.

8.1 Inclusion criteria

Healthy participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Healthy males.
2. Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
3. Age 18 to 55 (inclusive) years of age at the time of signing informed consent.
4. Body mass index (BMI) of 18.0 to 30.0 kg/m^2 as measured at screening.
5. Body weight not less than 50 kg.
6. Non-smokers (defined as has not used nicotine-containing products including e-cigarette for at least 3 months prior to the first dose as confirmed by cotinine test).
7. Must be willing and able to communicate and participate in the whole study.
8. Normal blood pressure (BP): Systolic BP (SBP) between 90 and 140 mmHg (inclusive), diastolic BP (DBP) between 45 and 90 mmHg (inclusive), measured after 10 min rest in supine position at screening and first admission (Day -1).
9. A resting heart rate (HR) between 45 and 90 bpm (inclusive), measured after 10 min rest in supine position at screening and first admission (Day -1).
10. ECG recording without clinically significant abnormality, including Fridericia's corrected interval between Q and T waves (QTcF) measure of ≤450 msec at screening and first admission (Day -1).
11. Participants must be able to swallow multiple capsules.

8.2 Exclusion criteria

Healthy participants who meet any of the following exclusion criteria are not to be enrolled in this study:

1. Have participated in an investigational trial involving administration of any investigational compound within 90 days prior to the study dosing or 5-times the half-life of the drug tested in the previous clinical trial, whichever is longer (time calculated relative to the last dose in the previous clinical trial).
2. History of any drug or alcohol abuse in the past 2 years.
3. Regular alcohol consumption >14 units per week and (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type) as confirmed by a positive alcohol breath test at screening or any on admission to the CRW.
4. Participants who do not have suitable veins for multiple venepunctures/cannulations as assessed by the Investigator or delegate at screening.
5. Clinically significant abnormal clinical chemistry, haematology, urinalysis, or clinically significant abnormal physical examination findings as judged by the Investigator.
6. Abnormal renal function (estimate glomerular filtration rate [eGFR] <90 mL/min).

7. Confirmed positive drugs of abuse urine test result (including but not limited to, amphetamines, tetrahydrocannabinol, morphine, methamphetamine, ketamine and benzodiazepines) and at any time during the study.
8. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) results.
9. Positive COVID test at screening and at admission of hospitalisation.
10. COVID-19 full vaccination to be received less than 21 days before Day 1, or start of vaccination, or second dose or booster of vaccination planned during the study period.
11. Clinically significant medical condition and/or abnormal laboratory results that could, in the opinion of the Investigator, jeopardize the participant's safety or participation in the study.
12. Known serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients in the past.
13. Presence or history of clinically significant allergy requiring treatment (including asthma, urticaria, clinically significant allergic rash or other severe allergic diathesis), as judged by the Investigator. Hay fever is allowed unless it is active.
14. Donation or loss of greater than 400 mL of blood within the previous 3 months or more than 100 mL within 30 days before signing informed consent form (ICF) to this trial.
15. Participants who are taking any prescribed drug in the 30 days before screening or require regular use of any prescription medication during the study.
16. Participants who have taken, any OTC medications, including vitamins, analgesics or antacids, herbal remedies, St. John's wort or diet complements (plants and vitamins that may be used for *e.g*. weight control or improve digestion or for "detox"... *e.g*., found in the composition extracts of ginkgo biloba, aesculus, cassia, harpagophytum, curcuma, elderberry, Vitis vinifera, cypress (Cupressus sempervirens)) in the 30 days before investigational medicinal product (IMP) administration. Exceptions may apply on a case-by-case basis, if considered not to interfere with the objectives of the study, as determined by the Principal Investigator (PI).
17. Use of enzyme-altering drugs (*e.g*. barbiturates, phenothiazines, cimetidine) within 30 days or 5 half-lives, whichever is longer, of study Day 1.
18. Use of products containing quinine (*e.g*., tonic water), grapefruit products, pomelo products, Seville orange products, supplements containing citrus aurantium and bitter orange in the 30 days prior to study Day 1.
19. CYP2D6 poor metabolisers, based on genotyping of DNA from blood samples.
20. Surgery within 12 weeks prior to screening, with the exception of appendectomy or at the discretion of the Investigator for minor surgery.
21. Any surgery (*e.g.* gastric bypass) or medical condition that may affect absorption of orally administered drugs.
22. Failure to satisfy the Investigator of fitness to participate for any other reason.

8.3 Participant identification

The assignment of number and code for participant's identification will be chosen to ensure anonymity.

Participant numbers will be allocated on the morning of the first dosing according to the code 001 to 020 using the lowest number available.

8.4 Method of participant assignment

Participants will be numbered consecutively in the order of their inclusion in the study. Participants will be identified to the Sponsor only by their assigned number.

The participant identification numbers will be assigned for all participants who are eligible to take part in the study, in accordance with inclusion and exclusion criteria, using the lowest participant number available. These numbers will be used as a mean of keeping the participant's identity confidential.

A list identifying the participants by participant number and initials will be kept in the study file.

All the participants enrolled in the study will receive the same treatment.

In case of drop-out before the first dose administration, the replacing participants will be assigned the same participant number. To allow these replacements, up to 4 reserved participants will be selected on addition to the 20 planned participants.

In case of drop-out after the first dose administration, participants will be replaced if necessary to have 16 evaluable participants following a decision taken jointly by the Investigator and the Sponsor.

8.5 Removal of participants from therapy or assessment

In accordance with the Declaration of Helsinki, participants will be free to withdraw from the study at any time if they wish to do so, for any reason specified or unspecified.

The following reasons will be accepted for study discontinuation:

- Withdrawal of participant consent, or loss to follow-up, or inability to remain under medical observation including post study examination. A participant will be considered lost to follow-up if he fails to return for scheduled visits and cannot be contacted by the CRW. If a participant fails to return to the CRW for a required study visit:
    - The CRW must attempt to contact the participant and reschedule the missed visit as soon as possible.
    - Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (*e.g.* 3 telephone calls on 3 separate occasions and, if necessary, an email or letter to the participant's last known email/postal address). These contact attempts should be documented in the participant's source.
    - If the participant cannot be contacted, he will be considered lost to follow-up.
- Non-compliance or major deviation from the protocol,
- Occurrence of a serious AE (SAE),
- Any other situation where, in the opinion of the Investigator or the Sponsor, continuation of the study would not be in the interest of the participant,
- Discontinuation of the study by the Sponsor.

The electronic case report form (e-CRF) has to be completed up to the time of drop out. All drop-outs after the first intake of the study drug should be given a post-study assessment (between 7 and 10 days after last administration but not less than 7 days).as appropriate. The premature termination form in the e-CRF must be completed for all drop-outs.

All data, including any drug concentrations from any withdrawn participant, have to be included in the final report. These data will only be evaluated if both the Sponsor and the Investigator agree that it is valid to do so.

Participants withdrawn because of AEs will undergo a physical examination and laboratory tests planned at the EoS visit. A follow-up of AEs will also be undertaken for withdrawn participants until AEs are resolved or the Investigator assesses them as chronic or stable or the participant's participation in the study ends *(i.e.* until a final report is completed for that participant, or the last contact with the participant).

8.5.1 General stopping criteria of the entire trial

The study will be discontinued if any unacceptable safety findings are identified in healthy participants included in the study. This decision will be made jointly by the PI and the Sponsor.

Both the Sponsor and the Investigator reserve the right to terminate the study at any time prior to inclusion of the intended number of healthy participants, but they intend to exercise this right only for valid scientific or administrative reasons. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of participant's interest.

Reasons for early termination by the Sponsor(s) may include but not be limited to:

- Too low enrolment rate.
- Protocol violations.
- Inaccurate or incomplete data.
- Unsafe or unethical practices.
- Questionable safety of the test article.
- Following the recommendation of IEC.
- Administrative decision.

Reasons for early termination by the Investigator may include but not limited to:

- Insufficient time or resource to conduct the study.
- Lack of eligible healthy participants.
- Unsafe to continue the trial.
- Following the recommendation of IEC or regulatory.

In the event that a study is early terminated either by the Sponsor or by the Investigator, the Investigator has to:

- Complete all e-CRFs to the greater extent possible.
- Return all test articles, e-CRF, and related study materials to the Sponsor who provided them.
- Answer all questions of the Sponsors or their representatives related to data of healthy participants enrolled at the site prior to study termination.
- Ensure that healthy participants enrolled in the study who had not yet reached a follow up time point are followed up with the necessary medical care.
- Provide in writing the reasons for his decision to the national health authority and the Sponsor.

9 ETHICS

9.1 Ethical conduct of the study

It is the responsibility of the Investigator, by delegation of duties of the Sponsor, to assure that all aspects of the ethics review are conducted in accordance with the Ethical principles stated in the Declaration of Helsinki (64th World Medical association (WMA) General Assembly, Fortaleza, October 2013) and/or the national laws, whichever provides the greatest level of protection for the study participants.

Written approval should be obtained from an Independent Ethic Committee (IEC) prior to the study being implemented.

The study will be conducted in accordance with International Guidelines on Good Clinical Practices (GCP)[8], Malaysian Good Clinical Practice (MGCP) and Standard Operating Procedures (SOP) for clinical investigation and documentation in force at CRW, in Hospital Ampang (clinical centre).

The study will be monitored by a monitor designated by the Sponsor who will regularly check compliance with the protocol, will compare selected key data in the e-CRF with source data, and will verify the drug accountability and all ICFs.

9.2 Ethics committee submission

The clinical study protocol and any information supplied to the participant to obtain informed consent, including written ICF, participant recruitment procedures (*e.g*. advertisements) and written information to be provided to healthy participants (information leaflets). Investigator brochure, and any other relevant study documents must be reviewed and approved by a qualified IEC prior to enrolment of participants in the study.

Prior to initiation of the study, the Sponsor must receive documentation of the IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

When necessary, the protocol amendments and revision of ICF will also have to be submitted to the IEC either for information or for formal approval.

Investigators must submit progress reports to the IEC in accordance with the IEC requirements. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the Sponsor. When the Sponsor provides the Investigator with a safety report, the Investigator must promptly forward a copy to the IEC.

After completion or termination of the study, the Investigator must submit a summary report to the IEC and to the Sponsor. The Investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IEC.

Copies of the study protocol and amendment(s) if any, as well as the approval of the IEC will be documented in the clinical study report (CSR).

9.3 Laws and regulation

The Investigator is responsible for conducting the study in accordance with the protocol, all applicable laws, regulations and GCP according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

9.4 Participant informed consent form

Preparation of the ICF is the responsibility of the Sponsor or designee and must include all elements required by the ICH, GCP and applicable regulatory requirements and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The Sponsor or designee must review and approve all changes to site-specific ICFs. The ICF must include a statement that the Sponsor or designee and regulatory authorities have direct access to participant records. Prior to the beginning of the study, the Investigator must have the IEC written approval/favourable opinion of the written ICF and any other information to be provided to the healthy participants.

Before being enrolled in the clinical study, healthy participants must consent in writing to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them. An informed consent document that includes both information about the study and the consent form will be prepare and given to the participant. This document will contain all the elements required by the GCP guideline ICH E6 and any additional elements required by local regulations. The document must be in a language understandable to the participant.

Healthy participants are free to withdraw from the study at any time during the study without stating any reasons. In the event if the PI received any new information from the Sponsor which may significantly affect the participant's risk to continue the study, the same information should be shared with healthy participants and re-consent shall be received from healthy participants.

A copy of the signed consent document must be given to the participant. The original signed consent document will be retained by the Investigator.

The Investigator will not undertake any assessment required for the present clinical study, until valid consent has been obtained.

10 CLINICAL SUPPLIES

10.1 Description, identification and storage

10.1.1 Acoziborole

Acoziborole will be supplied as oral tablet containing 320 mg.

10.1.2 Midazolam

Midazolam will be supplied as syrup at 2 mg/mL.

10.1.3 Dextromethorphan

Dextromethorphan will be supplied as syrup at 3 mg/mL.

The description of the study drugs is detailed in

Table 2.

Table 2 Description of the study drugs

	Acoziborole	Midazolam	Dextromethorphan
Name	-	Midazolam-ratiopharm	Bechilar
Formulation	Tablet	Syrup	Syrup
Strengths	320 mg per tablet	2 mg/mL	3 mg/mL
Route	Oral	Oral	Oral
Supplier	Creapharm	Ratiopharm	Montefarmaco

10.2 Packaging and labelling of drugs

All study drugs will be labelled according to the requirements of local law and legislation.

Acoziborole tablets will be packaged in aluminium foil blister pack with 3 tablets per blister.

Midazolam will be packaged in glass bottle containing 30 mL of solution.

Dextromethorphan will be packaged in glass bottle containing 100 mL of solution.

10.3 Randomisation

This is an open-label, non-randomised study and all the participants will receive the same treatment. Therefore, a randomisation schedule will not be produced.

10.4 Dosage and administration

Treatment will be administered in fasting conditions (*i.e.*, after an overnight fast of at least 10 h with no food permitted for 4 h post-dose).

Each participant will receive the following treatments:

- A single oral dose of 15 mg of dextromethorphan on Day 1 (Period 1),
- A single oral dose of 5 mg of midazolam on Day 8 (Period 1),
- A single oral dose of 960 mg of acoziborole, as 3 tablets of 320 mg, on Day 12 (Period 2),
- A single oral dose of 15 mg of dextromethorphan on Day 14 (Period 2),
- A single oral dose of 5 mg of midazolam on Day 21 (Period 2).

Both syrups of dextromethorphan and midazolam will be administered with a syringe. Approximately 240 mL of ambient temperature water will be given after complete administration of the syrup. Tablets of acoziborole will be administered with approximately 240 mL of ambient temperature water.

Participants will be dosed whilst standing or semi-recumbent or sitting position and will not be allowed to lie flat for 4 h post-dose, except for study procedures or if clinically indicated.

10.5 Treatment compliance

The following measures will be enforced to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified CRW staff,

- Immediately after dose administration, visual inspection of the oral cavity and hands (for study drug tablet) will be performed for each participant.

10.6 Storage of the study drugs

The study drugs will be stored in a secure limited access area in accordance with required storage conditions. The study pharmacist at CRW will be responsible for the correct storage and handling of the study products.

Acoziborole should not be stored above 30°C. Midazolam and dextromethorphan should be stored at 15-25°C.

All study drugs should be stored according to their package insert or Investigator Brochure. They should not be refrigerated or frozen.

Temperature monitoring *e.g*. temperature of the storage location will be monitored daily and recorded. Temperature excursions should be informed to the study monitor.

10.7 Dispensing of the study drugs

The Sponsor will supply the Investigator with acoziborole, midazolam and dextromethorphan as agreed upon for the timely completion of the clinical study described above.

The study Investigator or designee will be responsible for preparing the study treatments.

Study drugs will be dispensed only under the restricted conditions defined in the present protocol and according to ICH GCP guidelines and applicable local laws. They will only be administered by the Investigator or his delegate. Time of administration and initials of the person administering the study drugs will be documented in the e-CRF.

10.8 Drug accountability

Upon receipt of the study drugs, the Investigator or designee will send to the Sponsor the corresponding acknowledgement of receipt form. This form must be duly filled (including the date of receipt) and signed by the Investigator or designee. A drug movement form of all medication dispensed during the study will be maintained and must be readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

All investigational materials (medication and packaging) unused in the study will be returned to the Sponsor or sent to destruction with the Sponsor's approval before or at the termination of the study, together with an accountability form documenting:

- All administered units,
- All unused treatments,
- All units returned or destroyed at the end of the study, and the date of return or destruction.

11 STUDY PROCEDURES AND METHODS

11.1 Hospitalisation

The participants are planned to be hospitalised in the CRW on 2 occasions:

- On Period 1 from the day before the first dose of dextromethorphan until 24 h after the first dose of midazolam (*i.e*. from Day -1 to Day 9 morning),

- On Period 2 from the day before the single administration of acoziborole until 24 h after the last dose of midazolam (*i.e*. from Day 11 to Day 22 morning).

The Investigator will check on all participants' well-being prior to their discharge from the CRW. If relevant, participants will remain in the CRW until any AE causing concern has been resolved.

Overall, the expected duration of participant's participation will be 8 weeks.

11.2 Diet

The consumption of products containing quinine (*e.g*. tonic water), grapefruit products, pomelo products, Seville orange product, supplements containing citrus aurantium and bitter orange and diet complements (plants and vitamins that may be used for *e.g*. weight control or improve digestion or for "detox" ... *e.g*. found in the composition extracts of ginkgo biloba, aesculus, cassia, harpagophytum, curcuma, elderberry, Vitis vinifera, cypress (cupressus sempervirens)) will not be allowed from 30 days prior to Day 1 until discharge of the last treatment visit.

Smokers including e-cigarettes' users are not allowed to participate in the study.

During the 24 h preceding the first administration and up to EoS, participants will abstain from drinking alcohol, coffee, tea or beverages containing methylxanthines *(i.e.* theophylline, caffeine or theobromine).

Prior to each administration, participants will fast overnight for a minimum of 10 h.

On administration days, *i.e*. Day 1, Day 8, Day 12, Day 14 and Day 21, the first meal will be well-balanced in carbohydrates, lipids and proteins. A lunch will be served at 4 h 10 min post-dose. A snack will be served at 7 h 10 min post-dose. A dinner will be served at 11 h post-dose. A supper (snack) will be served at 13 h post-dose Participants will be allowed 30 min to eat lunch and dinner.

On the other days, the participants will be served breakfast, lunch, snack, dinner and supper (snack) at regular intervals. If a study assessment is to be performed at a time when a meal is planned to be served, meal will be served after completion of this assessment.

During the wash-out period, participants will not be allowed to consume any of banned products planned for all the study and a regular food intake will be recommended.

Participants will be only allowed to drink water. No fluids will be taken from 1 h prior to drug administration and up to 2 h post-dose. Water supply will be a minimum of 1500 mL for each 24 h period, as one bottle of mineral water, in order to allow the best normalization of water intake.

11.3 Exercise

Participants will be requested not to undertake vigorous exercise from 7 days before the first dose administration until after the post-study assessments.

11.4 Blinding

This is an open-label, non-randomised study and therefore blinding is not required.

11.5 Prior and concomitant therapy

11.6 Timing of study assessment and test

The detailed assessment schedule is presented in Table 1, Section 7.3.

When multiple assessments are scheduled at the same time point, the priority of each will be as follows, with the highest priority listed first:

1. Dosing of acoziborole, midazolam and dextromethorphan should be at 0 h.
2. Blood samples for analysis of plasma concentrations should be taken within 1 h before dosing for pre-dose samples or should be taken at exact time for post-dose samples.
3. 12-lead ECG will be performed in a supine position after at least 10 min of rest and before any blood draws.
4. Vital signs (BP, HR, and body temperature) will be performed in a supine position after at least 10 min of rest.
5. Urine samples can be collected either before or after other evaluations.
6. Physical examinations can be conducted either before or after other evaluations.

11.6.1 Screening procedures

All participants will undergo a screening visit between 1 and 28 days prior to the first study drug administration.

Before screening, participants will provide with their written consent to perform screening procedures and to establish their eligibility to participate in the study. The information recorded for all screened participants, regardless of their suitability for the study, will be retained and archived.

The following information and procedures will be performed and recorded as part of the screening assessments:

- ICF explanation collection,
- Medical and surgical history, previous medication,
- COVID-19 rapid test,
- Demographic data collection,
- Height, weight,
- Alcohol breath test,
- Cotinine test,
- Vein assessment,
- Physical examination as detailed in Section 11.7.1,
- Vital signs as detailed in Section 11.7.2,
- Resting 12-lead ECG (electronic records) as detailed in Section 11.7.3,
- Clinical laboratory evaluations, urinalysis, urinary drug screen, serology investigations as detailed in Section 11.7.4,
- CYP2D6 genotyping,
- Checking of the eligibility criteria.

11.6.2 Treatment period

11.6.2.1 Day -1

The participants will be admitted in the CRW on Day -1 and remain in the CRW until 24 h after the first administration of midazolam (*i.e.* Day 9 in Period 1) and following a satisfactory clinical assessment by the Investigator.

The following procedures will be performed:

- Checking of the eligibility criteria and compliance assessment,
- Medical and surgical history and prior medication update, if any,
- COVID-19 rapid test,
- Physical examination,
- Alcohol breath test,
- Vital signs,
- 12-lead ECG,
- Clinical laboratory evaluations, urinalysis, and urinary drug screen,
- AE monitoring,
- Concomitant medication.

11.6.2.2 Day 1

The following procedures will be performed:

Pre-dose

- Complaint directed physical examination,
- Blood sample for dextromethorphan and its active metabolite concentrations determination at pre-dose,
- Vital signs
- Administration of dextromethorphan,

Post-dose

- Blood sample for dextromethorphan and its active metabolite concentrations determination at 30 min, 1.0, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0 and 12.0 h post-dose,
- Concomitant medication recording,
- AE monitoring.

11.6.2.3 Day 2 to Day 4

The following procedures will be performed:

- Complaint directed physical examination,
- Vital signs,
- Blood sample for dextromethorphan and its active metabolite concentrations determination at 24 (Day 2), 36 (Day 2), 48 (Day 3) and 72 (Day 4) h post-dose,
- Blood sample for hormone level on Day 2, Day 3, and Day 4,
- Concomitant medication recording,
- AE monitoring.

11.6.2.4 Day 5 to Day 7

The following procedures will be performed:

- Complaint directed physical examination,
- Vital signs

- Concomitant medication recording,
- AE monitoring.

11.6.2.5 Day 8

The following procedures will be performed:

Pre-dose

- Complaint directed physical examination,
- Vital signs,
- Blood sample for midazolam and its active metabolite concentrations determination at pre-dose,
- Administration of midazolam,

Post-dose

- Blood sample for midazolam and its active metabolite concentrations determination at 15 min, 30 min, 1.0 h, 1 h 30 min, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0 and 12.0 h post-dose,
- Concomitant medication recording,
- AE monitoring.

11.6.2.6 Day 9

The following procedures will be performed:

- Physical examination,
- Vital signs,
- 12-lead ECG,
- Blood sample for midazolam and its active metabolite concentrations determination at 24.0 h post-dose,
- Concomitant medication recording,
- AE monitoring.

After completion of assessments, participants are discharged for the wash-out period. The participants are requested to come back for Period 2 on Day 11.

11.6.2.7 Day 11

The participants will be admitted in the CRW on Day 11 and remain in the CRW until 24 h after the last administration of midazolam (*i.e*. Day 22) and following a satisfactory clinical assessment by the Investigator.

The following procedures will be performed:

- Compliance assessment,
- COVID-19 rapid test,
- Physical examination,
- Alcohol breath test,
- Vital signs,
- 12-lead ECG,
- Clinical laboratory evaluations, urinalysis, and urinary drug screen,

- Concomitant medication recording,
- AE monitoring.

11.6.2.8 Day 12

The following procedures will be performed:

Pre-dose

- Complaint directed physical examination,
- Vital signs,
- Blood sample for acoziborole concentrations determination at pre-dose,
- Blood sample for hormone level determination,
- Administration of acoziborole,

Post-dose

- Concomitant medication recording,
- AE monitoring.

11.6.2.9 Day 13

The following procedures will be performed:

- Complaint directed physical examination,
- Vital signs,
- Concomitant medication recording,
- AE monitoring.

11.6.2.10 Day 14

The following procedures will be performed:

Pre-dose

- Complaint directed physical examination,
- Vital signs,
- Blood sample for acoziborole concentrations determination,
- Blood sample for dextromethorphan and its active metabolite concentrations determination at pre-dose,
- Blood sample for hormone level,
- Administration of dextromethorphan,

Post-dose

- Blood sample for dextromethorphan and its active metabolite concentrations determination at 30 min, 1.0, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0 and 12.0 h post-dose,
- Concomitant medication recording,
- AE monitoring.

11.6.2.11 Day 15 to Day 17

The following procedures will be performed:

- Complaint directed physical examination,
- Vital signs,
- Blood sample for dextromethorphan and its active metabolite concentrations determination at 24 (Day 15), 36 (Day 15), 48 (Day 16) and 72 (Day 17) h post-dose,
- Concomitant medication recording,
- AE monitoring.

11.6.2.12 Day 18

The following procedures will be performed:

- Complaint directed physical examination,
- Vital signs,
- Blood sample for acoziborole concentrations determination,
- Concomitant medication recording,
- AE monitoring.

11.6.2.13 Day 19 to Day 20

The following procedures will be performed:

- Complaint directed physical examination,
- Vital signs,
- Concomitant medication recording,
- AE monitoring.

11.6.2.14 Day 21

The following procedures will be performed:

Pre-dose

- Complaint directed physical examination,
- Vital signs,
- Blood sample for hormone level,
- Blood sample for acoziborole concentrations determination,
- Blood sample for midazolam and its active metabolite concentrations determination at pre-dose,
- Administration of midazolam,

Post-dose

- Blood sample for midazolam and its active metabolite concentrations determination at 15 min, 30 min, 1.0 h, 1 h 30 min, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0 and 12.0 h post-dose,
- Concomitant medication recording,
- AE monitoring.

11.6.2.15 Day 22

The following procedures will be performed:

- Physical examination,
- Vital signs,
- 12-lead ECG,
- Blood sample for midazolam and its active metabolite concentrations determination at 24.0 h post-dose,
- Clinical laboratory evaluations, urinalysis,
- Concomitant medication recording,
- AE monitoring.

After completion of assessments, participants are discharged. The participants are requested to come back for EoS visit.

11.6.3 EoS visit

The EoS visit will be performed between 7 and 10 days after last dose of midazolam on Period 2 but not less than 7 days. The following procedures will be performed:

- Physical examination,
- Body weight,
- Vital signs,
- 12-lead ECG,
- Clinical laboratory evaluations, urinalysis,
- Concomitant medication recording,
- AE monitoring.

11.6.4 Total blood volume

For each participant, the volumes of blood to be withdrawn from the screening to the EoS visit are presented in

Table 3. A total of 337.5 mL is planned to be withdrawn throughout the study. Nevertheless, some additional blood samples could be withdrawn if necessary for safety reasons or to repeat clinical laboratory evaluations.

Table 3 Volumes of blood

Sample type	Blood volume
Clinical laboratory evaluations (Total)	125 mL
Biology/Haematology	5 x 12 mL = 60 mL
Hormones	6 x 10 mL = 60 mL
Viral serology	2 mL
Genotyping	3 mL
PK samples	
Dextromethorphan and its metabolite	28 x 3 mL = 84 mL
Midazolam and its metabolite	26 x 3 mL = 78 mL
Acoziborole	4 x 6 mL = 24 mL
Discarded Heparinized Blood	
Dextromethorphan and its metabolite	26 x 0.5 mL = 13 mL
Midazolam and its metabolite	24 x 0.5 mL = 12 mL
Acoziborole	3 x 0.5 mL = 1.5 mL
Actual total	337.5mL

11.7 Participant evaluation

11.7.1 Physical examinations

A physical examination should include general appearance, skin, head and neck, eyes, ears, nose, throat, lymph node palpation, lungs, heart, chest, abdomen, neurological function.

Furthermore, a complaint directed physical examination will be performed when the participants complain of symptoms.

Physical examinations and complained directed physical examination will be performed at the time points detailed in Section 7.3.

11.7.2 Vital signs

Vitals signs include HR, SBP and DBP, respiratory rate and ear body temperature.

BP, HR and respiratory rate will be measured using an automatic device, after the participant has rested comfortably for at least 10 min in supine position. Measurements will be recorded directly on the source documents.

If values are out of range, repetition of measurements is allowed 2 times. Manual measurement shall be used after 2 erroneous automatic device reading.

Vital signs will be performed at time points detailed in Section 7.3.

11.7.3 ECG recordings

ECGs for safety purpose will be performed using the internationally recognized 12 leads with devices recorder after 10 min rest in supine position and before any blood draws. ECG will be recorded at a standard paper

speed of 25 mm/s and gain of 10 mm/mV. Print-outs for each ECG will include: date, time, initials of the Investigator or its deputy.

The ECGs will be performed in 6 × 2 leads during this study. The corresponding source data will consist of the ECG recorder paper print-outs.

The ECGs will be read and analysed by the Investigator.

ECG will be performed at time points detailed in Section 7.3.

11.7.4 Clinical laboratory tests

A local laboratory will analyse and report all laboratory safety tests performed in this study. Laboratory data from the local laboratory will be reported to CRW as paper printouts and/or electronic reports. Laboratory data will be reported to the Sponsor in a manner that anonymity of participants will be maintained. Data will be transferred by appropriate methods to the Clinical Data System.

Clinical laboratory tests will be performed according to the local regulations.

Haematology, biochemistry and urinalysis analysis will be performed at time points detailed in Section 7.3.

Laboratory parameters investigated in the study are listed in Table 4.

In addition, as part of safety assessment:

- Serology and genotyping will be performed at screening.
- Cotinine test will be performed at screening.
- COVID-19 rapid testing, urine drug screen, alcohol breath test will be performed at screening, on Day -1 and on Day 11.

Table 4 Laboratory parameters

Covid test	
CYP2D6 Genotyping	
Haematology	• Haemoglobin • Red blood cell (RBC) • Hematocrit • Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean cell hemoglobin concentration (MCHC), • Red cell distribution width (RDW) • WBC including differential • Platelet counts
Clinical Chemistry (Serum/Plasma)	• Alkaline phosphatase (ALP) • Alanine aminotransferase (ALAT) • Aspartate aminotransferase (ASAT) • Gamma–glutamyltranspeptidase (GGT) • Creatine phosphokinase (CPK) • Total, direct and indirect bilirubin • Total protein • Albumin • Creatinine and eGFR • Fasting glucose • Urea • Electrolytes (calcium (Ca^{2+}), sodium (Na^{+}), potassium (K^{+}), chlorides (Cl^{-})) • Bicarbonates
Hormones	• Serum cortisol • Plasma ACTH • Serum aldosterone • Serum DHEA-S • Serum androstenedione • Serum testosterone
Urine standard stick test	• Glucose • Ketones • Density • Occult blood • pH • Proteins • Leukocytes • Bilirubin • Urobilinogen • Nitrites
Urine drug screen	• Amphetamines (AMP), tetrahydrocannabinol (THC), morphine (MOP), methamphetamine (MET), ketamine (KET) and benzodiazepines (BZO)
Serology	• HBsAg • HCV antibody • HIV 1 & 2 antibodies

11.7.5 AEs

The Investigator will closely monitor any adverse event (AE) and will adopt the necessary clinical measures to ensure the safety of the participants.

AE assessment will be performed throughout the trial once the participant has been scheduled for treatment. See Section 11.8 for AEs definition and management.

11.8 Adverse events definitions and reporting

11.8.1 Adverse event definition

An AE is defined as:

"Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product, and which does not necessarily have a causal relationship with that treatment.

It can therefore be any unfavourable and unintended sign (for *e.g*. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."

Definition of an AE includes worsening (in severity and frequency) of pre-existing conditions ("Medical history") before first IMP administration and abnormalities of procedures (*i.e.,* ECG, X-ray, ophthalmologic or neurological examination etc.) or laboratory results which are assessed as "clinically significant".

What is not an AE

- Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are NOT considered as AEs.
- Symptoms, exacerbation or worsening of the studied disease will NOT be considered as AE nor captured on the AE page of the e-CRF if consistent with the anticipated natural progression of the disease (overall and for this given participant).
- Lack of efficacy of the IMP is not considered as AE.

11.8.2 Assessment of laboratory/procedures abnormalities

For every laboratory/procedure assessment, the Investigator will evaluate if the laboratory/procedure test is normal or abnormal. If abnormal (after repeat testing), the Investigator will assess if this finding is “clinically significant” or not.

An abnormal lab test must be compared with the previous value taking into account normal values in the studied population/country.

If a laboratory/procedure parameter is **abnormal AND** the abnormality assessed **clinically significant**, it should be reported as an AE.

An AE is a new event after the ICF signature or a worsening in the condition (in the case of laboratory/procedure tests, it is an increase in severity (clinical intensity) of the abnormality) which is judged clinically significant by the Investigator.

Laboratory/procedures (*e.g*. ECG...) abnormalities (or worsening in severity or frequency of pre-existing abnormalities) should be assessed as “clinically significant” (and therefore have to be reported as an AE) if they meet **at least one** of the following conditions:

- The abnormality suggests a disease and/or organ toxicity **AND** this abnormality was not present at the screening visit or is assessed as having evolved since the screening visit.

- The abnormality results in discontinuation of the study drug.
- The abnormality requires medical intervention or concomitant therapy.

When reporting an abnormal lab/procedure as an AE, a syndromic **clinical diagnosis should be recorded** rather than the abnormal value itself, if available (*e.g.*: acute pancreatitis instead of each finding separately: high levels of amylase, high levels of lipase, abdominal pain and vomiting, *e.g.*: "hypokalemia" rather than "decreased potassium levels"; "anaemia" rather than "decreased red blood cell count").

11.8.3 Serious adverse event (SAE)

An AE will be defined as serious if it:

- **results in death**

i.e. causes or contributes to the death.

- **is life-threatening**

in this context refers to an AE in which the participant was at risk of death at the time of the AE; it does not refer to an AE that hypothetically might have caused death if more severe.

- **requires in-participant hospitalisation or prolongation of existing hospitalisation**

i.e. the AE requires at least an overnight admission or prolongs a hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (*i.e*., plastic surgery) or per protocol or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion (*i.e*. if the protocol requires planned hospitalisation).

- **results in persistent or significant disability or incapacity**

i.e. the AE resulted in a substantial disruption of the participant's ability to conduct normal activities.

- **is a congenital anomaly / birth defect**

i.e. an AE outcome in a child or foetus of a participant exposed to the IMP before conception or during pregnancy.

- **is an important medical event, *i.e*. is medically significant**

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events/reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the participant or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious AE.

SAE onset/start date:

Start date of SAE or date when the AE becomes serious (see seriousness criteria of an SAE).

SAE end/stop date:

SAE end date is the date of AE recovery.

11.8.4 Eliciting adverse event information

The Investigator is required to report all directly observed AEs and all AEs spontaneously reported by the trial participant using concise medical terminology.

In addition, to avoid bias in eliciting AEs, each trial participant will be questioned about the occurrence of AEs (at each visit and throughout admission period as necessary), with general, non-leading questions such as" Since last visit have you had any health problem?" or "How are you feeling?".

All AEs (serious and non-serious) must be recorded on the source documents and e-CRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Sections 11.8.1, 11.8.5 and 11.8.8.

Information on AEs must be evaluated by a physician.

Each AE is to be classified by the Investigator as serious or non-serious (see definition of a SAE in Section 11.8.3). This classification will determine the reporting procedure for the event.

In addition, the frequency, seriousness (see Section 11.8.3), severity (see Section 11.8.6), and causality (see Section 11.8.7) assessment of AEs will be described. The frequency of AEs and AEs/SAEs leading to treatment discontinuation will be reported.

Non-serious AEs are to be reported on the e-CRF, including description of the event, onset date, duration, severity, seriousness, relationship to all study drugs, actions taken and outcome.

In the e-CRF, a given AE will be recorded only one time per participant, and the severity recorded will be the maximum level reached. If several distinct episodes of the same condition occur, their number will be recorded in the e-CRF.

SAEs will be reported both on the AE e-CRF and the SAE forms.

Non-serious AEs are to be reported on the e-CRF.

11.8.5 Adverse event reporting period

The AE reporting period begins upon participant enrolment in the trial (after signature of informed consent) and ends at EoS visit.

All AEs that occur during the AE reporting period specified in the protocol must be reported to DNDi, whether the event is considered medication related.

In addition, any serious AE that occurs subsequent to the AE reporting period that the Investigator assesses as related to the investigational medication should also be reported as an AE.

Screening failure: beyond the date of screening failure (to be recorded), only serious study-related events will be followed-up.

11.8.6 Grading of adverse event severity

For each serious and non-serious AEs, the Investigator is required to assess the severity of each AE.

It is to be noted the distinction between severity and seriousness of AEs. A severe AE is not necessarily a SAE.

The severity is a clinical determination of the intensity of a specific event. In clinical trials, the severity of AEs must be assessed by Investigators according to the following definitions:

Mild:	The participant is aware of the event or symptom, but the event or symptom is easily tolerated (*e.g.* no reduction in daily activities is required).
Moderate:	The participant experiences sufficient discomfort to interfere with or reduces his or her usual level of activity.
Severe:	Significant impairment of functioning: the participant is unable to carry out usual activities and/or the participant's life is at risk from the event.
Life-Threatening:	The participant is at significant risk of life; it does not refer to an event which hypothetically might have caused death if it were more severe (life-threatening consequences, urgent intervention required).
Death:	Death related to an event.

This information will be entered in the AE case report forms.

When the intensity of an AE changes over time, each change in intensity will be recorded in the source documents until the event resolves. However, only one AE and the maximum intensity will be recorded in the e-CRF for each separate event. If the AE resolves but then recurs, each will be recorded as a separate AE, with the appropriate start and stop times.

11.8.7 Adverse event causality assessment

For each serious and non-serious AEs, the investigator is required to assess the possible relationship between the adverse event and each trial drugs, i.e. to determine whether there exists a reasonable possibility that the trial drugs caused or contributed to the AE(s).

The following categories for relationship to treatment will be used during AE reporting:

Related	There is at least a reasonable possibility of a causal relationship between an AE and an investigational medicinal product. This means that there are **facts (evidence) or arguments** to suggest a causal relationship
Not related	There is no reasonable possibility of causal relationship.

To help Investigators with the decision binary tree (Related/Not related) in the evaluation of causality, the Council for International Organizations of Medical Sciences (CIOMS) VI group recommends that Investigators be asked to consider the following before reaching a decision:

- Medical history (including presence of risk factors),
- Lack of efficacy/worsening of existing condition,
- Trial medications,
- Other medications (concomitant or previous),
- Withdrawal of trial medication, especially following trial discontinuation / end of trial medication,
- Erroneous treatment with trial medication (or concomitant),
- Protocol related procedure.

Causality is to be assessed for each IMP.

11.8.8 Adverse event reporting requirements

Throughout the study, all AEs observed by either medical staff or professional collaborators or reported by the participant spontaneously or in response to a direct non-leading question, will be evaluated by the Investigator and noted in the AE section of the-e-CRF.

Information on AEs must be evaluated by a physician.

Each AE is to be classified by the Investigator as serious or non-serious. This classification will determine the reporting procedure for the event.

All SAE are to be reported immediately (**within 24 hours of awareness of SAE by the Investigator**) to DNDi via **SAEOXA07study@dndi.org**, using the SAE report form. This includes a description of the event, onset date and type, duration, severity, relationship to trial drugs, outcome, measures taken and all other relevant clinical and laboratory data.

The initial report is to be followed by submission of additional information (follow-up SAE form) as it becomes available. Any follow-up reports should be submitted as soon as possible, and if possible within 5 working days.

SAEs should also be reported on the clinical trial AE e-CRF. It should be noted that the form for reporting of SAE (SAE form) is not the same as the AE section of the e-CRF. Where the same data are collected, the two forms must be completed in a consistent manner, and the same medical terminology should be used.

The Investigator will record and report SAEs to the IEC in accordance with the applicable regulatory requirements.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR**) is a suspected AE related to an investigational medicinal product that is **both unexpected and serious**.

DNDi, the Sponsor is responsible for determining the expectedness of the event, using the reference safety information defined for this trial.

DNDi will notify the Regulatory Authorities of all SUSARs/other types of SAEs (If applicable) in compliance with local safety reporting requirements.

11.8.9 National Pharmaceutical Regulatory Agency reporting requirement

Fatal and life-threatening SUSAR will be notified to the National Pharmaceutical Regulatory Agency (NPRA) as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor that a case qualifies, followed by a report as complete as possible within 8 additional calendar days. The report will include an assessment of the importance and implications of the findings, including relevant previous experience with the same or similar medicinal product. Follow-up information will be actively sought and follow-up reports will be submitted to the NPRA when it becomes available.

SUSARs that are not fatal or life-threatening will be notified to the NPRA as soon as possible but no later than 15 calendar days after first knowledge by the Sponsor that a case meets the minimum criteria for expedited reporting. Follow-up information will be actively sought and follow-up reports will be submitted to the NPRA when it becomes available.

Initial reports submitted will meet the following minimal criteria (valid reports for safety reporting):

a. An identifiable participant
b. A suspected medical product
c. An identifiable reporting source

d. An event or outcome that can be identified as serious and unexpected

e. In clinical investigation cases, there is a reasonable suspected causal relationship

11.8.10 Adverse event follow-up

All AEs should be followed until

- they are resolved; or
- the Investigator assesses them as 'chronic' or 'stable'; or
- the participant participation in the trial ends (*i.e.*, until a final report is completed for that participant, or otherwise the last contact with the participant).

The following categories will be used to document outcome of each AE:

Action taken: None, drug treatment, participant withdrawn, other (specified).

Outcome: Completely recovered; recovered with sequelae; ongoing; death; unknown.

The decision to suspend, and resume treatment or to permanently interrupt treatment due to an AE will be left to the clinician in charge.

In addition, all SAEs (related or not) and those non-serious events assessed by the Investigator as related to the investigational drug must continue to be followed even after the participant participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the AE e-CRF and SAE form (if applicable).

Note: The recording of such events in the e-CRF/clinical database is not possible after the end of the trial (after database lock). Follow-up not recorded in the e-CRF will be reported in the CSR. In that case, the follow-up information should be reported to the organisation in charge of the pharmacovigilance of the trial and recorded in the safety database.

11.9 Safety criteria

All participants who will receive any dose of any study drug will be included in the safety evaluation. The evaluation of study drug safety will include review of clinical AEs and clinical laboratory AEs, as well as a review of vital signs, ECG results. Clinical observations and clinical laboratory data collected from the first dose administration until discharge of the study or participant discontinuation will be compared with baseline data obtained at screening or immediately before the first dose administration.

12 PHARMACOKINETICS

12.1 Blood samples

12.1.1 PK sampling

Venous whole blood samples will be collected from all participants (using direct venipuncture or an indwelling catheter).

To maintain the patency of cannula during the study, the cannula will be flushed with approximately 1.0 mL of heparinized saline after collection of PK samples. Prior to blood sampling, 0.5 mL of heparinized blood will be discarded (at every interval except for the pre-dose sample). In case of blockade in an existing cannula, extra heparinized saline may be injected to stimulate the cannula and later blood samples will be collected after discarding the heparinized blood.

Blood samples for assessment of acoziborole will be taken at the following time points in Period 2: pre-dose on Day 12 (before acoziborole administration), then on Day 14 (before dextromethorphan administration), on Day 18 and on Day 21 (before administration of midazolam).

If meals and blood collections coincide, blood will be collected before eating. The reference pre-dose blood (*i.e.* on Day 1, Day 8, Day 12, Day 14 and Day 21) should be taken anytime in the hour before administration.

Table 5 Tolerance windows for pharmacokinetic blood sampling

Time Point	Tolerance Window
Pre-dose	Within 1 hour
0 h – 4 h post dose	- 2 / + 2 min
> 4 h – 12 h post dose	- 3 / + 3 min
> 12 h – 24 h post dose	- 5 / + 5 min
> 24 h post dose	- 10 / + 10 min

Measurements performed within these tolerance windows will not be considered protocol deviations and will be documented in the CRF.

A total of 28 blood samples for dextromethorphan and its active metabolite, 26 blood samples for midazolam and its active metabolite, and 4 blood samples for acoziborole and an approximate volume of 186 mL, will be collected from each participant, over the study duration.

12.1.1.1 Dextromethorphan, midazolam and their active metabolites

Blood samples will be collected at the following time points:

- Blood samples for assessment of dextromethorphan and its active metabolite (dextrorphan) will be taken at: pre-dose, 30 min, 1.0, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0, 12.0, 24.0, 36.0, 48.0 and 72.0 h post-dosing for Period 1 and Period 2.
- Blood samples for assessment of midazolam and its active metabolite (1'-hydroxy-midazolam) will be taken at: pre-dose, 15 min, 30 min, 1.0 h, 1 h 30 min, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0, 12.0, 24.0 h post-dosing for Period 1 and Period 2.

A 3 mL blood sample will be collected into a EDTA tube. Blood samples will be centrifuged at 1500 g for 10 min at 4°C within 2 h of blood collection. The resulting plasma (about 1.2 mL) will be split into 2 storage tubes. Plasma samples will be frozen as soon as possible preferably within 1 h. Plasma samples must be stored at below -20°C.

12.1.1.2 Acoziborole

Blood samples for assessment of acoziborole will be taken at the following time points in Period 2: pre-dose on Day 12 (before acoziborole administration), then on Day 14 (before dextromethorphan administration), Day 18 and Day 21 (before administration of midazolam).

A 6 mL blood sample will be collected in CPDA tubes. Blood samples will be centrifuged at 1500 g for 10 min at 4°C within 1 h of blood sample collection.

Exactly 5 µL of formic acid will be transferred into 5 mL polypropylene tubes using a calibrated micropipette. The tube should be immediately capped to avoid evaporation of the formic acid. The tubes should then be centrifuged for approximately 2 min to ensure the formic acid is at the bottom of the tubes prior to addition of plasma.

Exactly 1 mL of plasma will be transferred into 2 appropriately labelled 5 mL polypropylene tubes pre-filled with exactly 5 µL of formic acid. Acidified plasma sample will be frozen as soon as possible after preparation (maximum 2 h after blood collection). Samples must be stored at or below -20°C until shipment.

12.1.2 Blood sampling for hormone level

Blood samples for hormone level will be collected at the following schedule:

- Day 2 (24 h post dose), Day 3 (48 h post dose), Day 4 (72 h post dose) in Period 1.
- Day 12, Day 14 and Day 21 in Period 2.

6 mL of blood will be collected in plain tube and 4 mL of blood will be collected in EDTA tube.

Samples will be collected for determination of concentration of selected hormones

- Serum cortisol
- Plasma ACTH
- Serum aldosterone
- Serum DHEA-S
- Serum androstenedione
- Serum testosterone

12.2 Sample handling and labelling

Each aliquot (blood, plasma tubes) will be identified as follows:

- Protocol No.,
- Participant No.,
- Type of sample,
- Day of collection,
- Theoretical sampling time,
- Analyte (dextromethrophan, midazolam, acoziborole).

12.3 Shipment of PK samples

Each set of aliquots for dextromethorphan and its metabolite and midazolam and its metabolites will be sent frozen separately to:

Kenneth Ho (Project Manager)
Info-Kinetics Sdn Bhd
5th Floor Gleneagles Penang, No. 1
Jalan Pangkor
10050 George Town
Pulau Pinang Malaysia
Phone: +6012-4285736
Email: Kennethho@info-kinetics.com

Each set of aliquots for acoziborole will be sent frozen separately to:

Valérie Wauthier
SGS Belgium
Vieux Chemin du Poète, 10
1301 Wavre - Belgium
Phone: +32 (0)10 42 11 90
Email: valerie.wauthier@sgs.com

For sample shipment, tubes must be packed according to International Air Transport Association (IATA) specifications. Each shipment must include a shipment manifest and completed freezer log form.

12.4 Analytical methods

Plasma samples will be analysed for dextromethorphan and its active metabolite and midazolam and its active metabolites by Infokinetics (Penang, Malaysia) using validated liquid chromatography mass spectrometry tandem (LC-MS/MS) methods.

Plasma samples will be analysed for acoziborole by SGS (Wavre, Belgium) using validated LC-MS/MS method.

Analytical methods will be detailed in bioanalytical reports.

12.5 PK analyses

The PK analysis will be carried out by PhinC Development. After completion of the bioanalytical part of the study, an electronic copy of the quality checked and validated data will be provided to PhinC Development.

PK analysis will be done after database lock using actual PK blood sampling times.

Plasma concentrations will be then processed throughout the PK software for PK data generation. The PK parameters will be calculated by non-compartmental analysis, using Phoenix WinNonlin® (Version 8.1 or higher- Certara -Princeton - USA).

For each calculation of the PK parameters and characteristics the following rules will be applied:

- All the plasma concentrations validated by the bioanalytical laboratory and provided to the pharmacokineticist will be used for the PK analysis.

- The actual blood sampling time points related to the preceding administration will be used.
- At time points in the lag-time between time zero and the first concentration equal or above limit of quantification (LOQ), concentrations below LOQ (BLQ) will be set to zero (0). Concentrations below LOQ between 2 concentrations equal or above LOQ will be considered as missing. Trailing concentrations BLQ will not be used in calculations.
- For plasma concentration above the upper limit of quantification and reported as ALQ in the final plasma concentration tables, ALQ will be considered as missing for the PK analysis.
- Not reported concentration (NR) will be excluded from the PK analysis.
- If pre-dose concentration is less than or equal to 5% of C_{max} value in a PK profile, the participant's data can be included in all PK measurements and calculations without any adjustments. If the pre-dose value is greater than 5% of C_{max}, the participant will be dropped from all statistical evaluations.
- For each participant, the following PK parameters will be derived for dextromethorphan and its metabolite on Day 1 (Period 1) and Day 14 (Period 2) and for midazolam and its metabolite on Day 8 (Period 1) and Day 21 (Period 2):

C_{max} The observed maximum concentration measured in plasma will be obtained directly from the concentration-time data.

t_{max} The time at which C_{max} is apparent, identified by inspection of the plasma drug concentration *versus* (*vs.)* time data by Phoenix WinNonlin®.

AUC_{0-24} The area under the concentration-time curve from time zero (pre-dose) to 24 h after administration will be calculated using a linear trapezoidal method (if at least 3 concentrations above LOQ).

AUC_{0-t} The area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration will be calculated using a linear trapezoidal method (if at least 3 concentrations above LOQ).

k_e The terminal plasma elimination rate-constant will be estimated from log-linear regression analysis of the terminal phase of the plasma concentration-time profile. The number of points included in the terminal phase will be determined by visual inspection of the semi-log plots of the plasma concentration-time profiles (at least 3 excluding C_{max}). The correlation coefficient for the goodness of the fit of the regression line through the data points (r^2) must be 0.9000 or higher, for the value to be considered reliable. No determination of $t_{1/2}$ or AUC extrapolation will be performed with unreliable elimination rate constants.

$t_{½}$ The apparent terminal elimination half-life will be calculated as $\ln 2/k_e$, where k_e is the elimination rate constant as defined above.

$AUC_{0-\infty}$ The AUC from time 0 to infinity will be calculated as $AUC_{0-\infty} = AUC_{0-t} + AUC_{t-\infty}$, where AUC_{0-t} is the area under the concentration-time curve as defined above and $AUC_{t-\infty} = C_t/k_e$, where C_t is the measured concentration at time of the last quantifiable concentration t. The extrapolated part of $AUC_{0-\infty}$ must be < 20% for the value be considered as reliable.

$\%AUC_{extra}$ Percentage of $AUC_{0-\infty}$ extrapolated.

For acoziborole only plasma concentrations will be presented.

13 DATA HANDLING AND STATISTICS

13.1 Justification of the sample size

Within participant coefficient of variation (CV) for midazolam was estimated from literature[6] to be around 25% +/-5%. In absence of specific information, the same range of CV was assumed for dextromethorphan.

Due to the pronounced effect of acoziborole anticipated on midazolam and dextromethorphan PK, the sample size is based on high precision for the estimates characterizing the interactions, *i.e*. the GMR with their confidence intervals (CI).

The study is designed to target 95% CI within 80% and 125% of the GMRs, for each treatment, with at least 90% statistical power.

Table 6 Sample size required to achieve the target precision of 80% to 125% of the GMR with a type I error of 5% (2-sided) and a statistical power of at least 90%

	Within participant CV (%)		
	20%	25%	30%
N per period	9	11	15

Considering a conservative CV of 30%, the targeted precision could be achieved with 16 participants (15 presented in Table 6 rounded to the highest even integer to allow a possible stratification if needed).

Whatever the sample size selected from Table 6, the power to elicit at least a two-fold increase or reduction in PK parameters will be above 90% at the two-sided 5% level. Sixteen (16) participants (15 rounded to the highest even integer to allow a possible stratification if needed) should be included.

13.2 Description of populations for analysis

The protocol deviations will be determined before database lock.

The following data sets will be used for the statistical analysis:

Safety: Includes all the participants who received at least one dose of the study medications.

PK: Two (2) PK populations will be defined:

- Dextromethorphan PK population which includes all the participants who receive both administrations of dextromethorphan and who complete the study at least up to Day 15 and did not have any protocol deviation or events resulting in a bias for the PK evaluation.
- Midazolam PK population which includes all the participants who receive both administrations of midazolam and who complete the study at least up to Day 22 and did not have any protocol deviation or events resulting in a bias for the PK evaluation.

13.3 Data recording

The e-CRFs will be prepared in Medrio and will be reviewed by the Data Management and Biostatistics department of DNDi-Africa Regional Office and approved by the trial team before the first participant first visit.

All data obtained during the course of the clinical phase of the study will be recorded directly and legibly into the source documents in black permanent ink.

13.4 Data Management

13.4.1 Database set-up

The database set-up and screens design are performed using MEDRIO Electronic data capture (EDC) database for management of this study's data.

MEDRIO EDC is an industry standard clinical data management system which is compliant with FDA 21 CFR Part 11 requirements as well as other regulatory requirements such as ICH/GCP, GDPR (General Data Protection Regulation) and HIPAA (The Health Insurance Portability and Accountability Act).

13.4.2 Data management plan

This document describes the data management activities and responsibilities for study as performed by staff members of Data Management and Biostatistics department of DNDi-Africa Regional Office.

The final version of the Data Management Plan (DMP) will be sent to the Sponsor for approval.

13.4.3 Data collection

All clinical data will be reported electronically by the Investigator or authorized designee on a web-based e-CRF. This e-CRF is specifically designed for the study and developed by the Data Management Department using MEDRIO a validated Electronic Records/Electronic Signature-compliant (21 CFR Part 11) application.

A unique number will identify the participants on the e-CRF.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information.

13.4.4 Responsibilities

The Investigator or authorized designee is responsible for the timeliness, completeness, and accuracy of all observations and other data pertinent to the clinical investigation in the e-CRFs.

The Investigator will ensure that all data are entered promptly after the evaluation has occurred, in accordance with source documents and specific instructions accompanying the e-CRFs, designed specifically for the study.

The Data Management and Biostatistics department will provide all tools, instructions, and training necessary to complete the e-CRF, and each user will use personal credentials (username and password) to enter the system.

The Data Management and Biostatistics department will be responsible for data processing, in accordance with the DNDi data management procedures. The related data management activities and requirements will be described in the DMP.

13.4.5 Data validation

Automatic checks and listings are designed and performed according to the data validation plan. In case of missing values, out of range values, data inconsistencies or values that fail logical checks, queries will be generated and submitted through the electronic data capture (EDC) system to the Investigator site for resolution.

Correction will be made either automatically from the immediate completion or following the review of the data during the monitoring or medical review. An audit trail, which will be initiated at the time of the first data entry, allows tracking all modifications.

The Data Management and Biostatistics Department may generate additional requests to which the Investigator must respond electronically by confirming or modifying the data questioned. The requests with their responses will be implemented into the e-CRFs.

13.4.6 Data coding

The study Adverse Events and medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Using MEDRIO's inbuilt coding module, the Data Manager will automatically code all the verbatim terms with values in the coding dictionary, as well as matching verbatim terms with synonyms that were defined previously.

Verbatim terms that do not code automatically will be manually coded by the study medical manager (SMM) or designee as per the guidelines of the MedDRA and the selected dictionary term saved as a Synonym to be used later for auto-coding of matching verbatim terms.

Concomitant medications will similarly be coded by the DM using the World Health Organization Drug Dictionary (WHODRUG) and any medications that do not code automatically will be manually coded by the SMM or designee as per the guidelines of the WHODRUG.

13.4.7 Database lock

Once validated, the database will be locked so that no more change will be possible on the frozen data. The database lock process will be detailed in the DMP.

13.4.8 Data transfer

Final validated data (SAS data sets) and participant data report will be transferred to the Sponsor via a secure file exchange platform after database lock.

13.5 Statistical analyses planned

A detailed statistical analysis plan (SAP) will be prepared by PhinC Development. This SAP should be validated by the Sponsor prior database lock.

The statistical package SAS® v9.4 will be used to produce all summary tables and data listings. The summary tables and data listings will be produced by PhinC Development.

In general terms, categorical data will be presented using counts and percentages of participants, while continuous variables will be presented using the arithmetic mean, standard deviation (SD), median, minimum (Min), maximum (Max), and number observations (N). The 95% CI will be also presented on changes from baseline. In general, Min and Max will be quoted to the number of decimal places as recorded in the e-CRF; mean, median and SD values will be quoted to one further decimal place. Percentages will be rounded to one decimal place.

Descriptive statistics will be calculated by period, day and time points when applicable.

Individual data listings will be presented sorted by participant number, period, day and time points when applicable

General rule for baseline, unless otherwise specified, will be to consider the last measurement before the first administration of the study medication (recheck, if any). Where rechecks of safety assessments will be performed, the original value will be used for analysis except where the original value has a reasonable explanation to be excluded from the calculation.

13.5.1 Demographics and other baseline characteristics

The following demographic and other baseline characteristics will be analysed:

- Demographic characteristics (including age, weight, height and BMI),
- Urinary drug screen,
- Alcohol breath test,
- Cotinine test,
- Serological assessment,
- COVID-19 test,
- Genotyping,
- Previous dosing and ongoing medication,
- Medical history.

All demographics and other baseline characteristics will be individually listed.

Descriptive statistics will be performed on demographic characteristics for each analysis set (if different). Other parameters will be summarized using appropriate statistics (if applicable).

No significance testing of demographic data will be performed

13.5.2 Safety analysis

Safety and tolerability data will be summarized using the following parameters:

- Vital signs,
- 12-leads ECG,
- Haematology,
- Clinical chemistry,
- Urinalysis,
- Physical examination,
- Body weight,
- AEs.

No formal hypothesis testing of these parameters will be carried out.

13.5.2.1 Vital signs, 12-leads ECG parameters and body weight

Vital signs and ECG parameters (HR, interval between P and R waves (PR), interval between Q and S waves (QRS duration), QT interval, QTcF) will be individually listed. Quantitative parameters outside reference ranges will be flagged on individual data listings.

These parameters will be summarised, on observed values and on changes from baseline values, depending on the parameter.

13.5.2.2 Haematology and biochemistry parameters

Biochemistry and haematology parameters will be individually listed. In addition, quantitative parameters outside reference ranges will be flagged on individual data listings.

These parameters will be summarised, on observed values and on changes from baseline values, depending on the parameter.

13.5.2.3 Urinalysis

Urine parameters will be individually listed and summarised by using appropriate statistics.

13.5.2.4 Physical examination

An individual data listing of abnormal physical examination findings will be provided. Abnormal physical examination findings will be summarised using appropriate descriptive statistics.

13.5.2.5 AEs

Throughout the study, all AEs observed by either medical staff or professional collaborators, or reported by the participant spontaneously or in response to a direct non-leading question, will be evaluated by the Investigator and noted in the AE section of the-CRF, as described in Section 11.8.

All the information related to the AEs (including MedDRA system organ class (SOC), preferred term (PT) and lowest preferred term) will be provided. Therefore, an individual data listing sorted by participant number, treatment and time of onset will include all events that a participant experiences.

An AE will be considered as treatment emergent (TEAE) if it appeared after the first treatment administration, or if appeared before dosing and worsened after dosing. In case of missing onset date of AE or missing onset time of AE when it appeared the first dosing day, the AE will be considered as TEAE.

All TEAEs will be displayed in summary tables, by MedDRA SOC and PT. The tables will present the number of participants for which the events occurred, and the rate of occurrence, expressed as a percentage of the number of participants in the safety population.

13.5.3 Blood sampling for PK analysis

Once the database is locked, the individual post-dose sampling times will be calculated by the biostatistician from the actual date and time of blood samplings and from the actual date and time of study drug administration.

13.5.4 PK data

The statistical analysis will be carried out by PhinC Development using the SAS® package (release 9.4) or using Phoenix WinNonlin® Version 8.1 or higher.

13.5.4.1 Descriptive statistics

For each compound, individual plasma concentrations will be presented by day, treatment (with or without acoziborole) and timepoints. Descriptive statistics for the plasma concentrations will be presented as number of observations (N), arithmetic mean, SD, and will be calculated if at least 2/3 of the plasma values per

timepoint are non-missing. For descriptive statistics calculations, concentrations BLQ will be set to zero (0) before the first concentration equal or above LOQ and considered as missing after.

For each compound, individual PK parameters will be presented by day and treatment (with or without acoziborole). Descriptive statistics of the PK parameters will be presented as N, mean, SD, CV%, median, geometric mean (GM), Min, and Max if N ≥ 3.

In the tables of individual PK parameters, all the deviations from planned analysis will be mentioned by flagging the abnormal results (*e.g.*, percentage of extrapolated AUC > 20%).

For each compound, a measured plasma drug concentration *vs*. actual time curve will be produced in graphic for each participant on both linear/linear and log/linear scales. Mean plasma drug concentration *vs*. nominal time curves will also be produced by treatment, separately.

13.5.4.2 Formal statistics

For midazolam and dextromethorphan separately, the log transformed PK parameters will be analysed using a mixed analyse of variance (ANOVA) model including fixed effect for treatment (*i.e*. with or without acoziborole) and the participant as random effect. The GMR (midazolam or dextromethorphan with/without acoziborole) and their 95% CI will be computed by back transforming the differences between treatments and their 95% CI obtained from the ANOVA in log scale.

13.5.5 Exploratory parameters (Hormones)

Hormone levels will be individually listed. These parameters will be summarised, on observed values and on changes from baseline values.

14 ETHICAL, REGULATORY AND ADMINISTRATIVE SECTION

14.1 Personal data processing

Applicable data privacy laws and regulations must be adhered to. The Investigator and the Sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements. Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

These rights are also guaranteed by the GDPR (EU) 2016/679.

14.2 Insurance

The Sponsor has taken out a liability insurance as required by local regulatory requirements.

DNDi is insured to indemnify the Investigator against any claim for damages brought by a research participant who suffers from research related injury during the performance of the trial according to the protocol.

14.3 Participant reimbursement fee

Healthy participants will be reimbursed adequate reimbursement fees on account of their participation in the study. In case of withdrawal of a participant before completion of the study, participant will be reimbursed a pro-rated fee based on the extent of participation.

14.4 Medical care

Any medication that is required during the study period will be provided free of charge to the participant. Food during the participant treatment phase will also be provided free of charge to the participant.

14.5 Confidentiality

The information in this document and in any future information supplied contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

Study and personal data will be stored in accordance with local and global data protection laws. Information on confidentiality is also contained in the ICF. Potential participants will be informed of the following:

- If a participant withdraw consent to participate in the study the Investigator will, unless required for participant safety, no longer use study data or share it with others. However, the Sponsor may still use study data, including a participant's personal information in pseudonymized form, that was provided before consent was withdrawn.
- Personal information about participants will be collected to conduct this study. This information will be recorded on source documents and e-CRFs. The e-CRFs will be identified by participant numbers only.
- The Sponsor may use study data to conduct the study, to support applications for approval of the study medication and for research related to the development of pharmaceutical products, diagnostics or medical aids.
- The Investigator and the Sponsor are each responsible for their handling of study data in accordance with applicable data privacy laws. When study data is processed by the Sponsor, it will be done by a unique identifier. The Sponsor may transfer the coded study data from Malaysia to other countries and may also share study data with other companies within its group (if applicable), with its service providers, its contractors and with research institutions, and research based commercial organizations who will use study data only for the purposes described above complying with all local and international data privacy laws and regulations to protect participants' personal and other information, even in countries where data privacy laws are less strict.
- All records identifying participants will be kept confidential and, to the extent permitted by the applicable laws and regulations, it will not be made available publicly. Also, in reports or publications produced from this study's data participants will be identified by coded numbers only.
- To confirm that the study data collected are correct and related to participants, selected people working for the Sponsor, independent auditors, as well as representatives of government regulatory authorities and the ethics committee(s) will have access to the participants' personal information at the study centre and that they are required to maintain the confidentiality of participants' information. Participants also have the right to ask the Investigator about their data and to have updates made to their personal health information.

The site may keep participant information in the site database. The data may also be photocopied. All copies will be stored by the site and the Sponsor on condition that national legislation with respect to protection of personal data is adhered to. The Investigator will maintain a participant identification list (participant numbers with the corresponding participant names) to enable records to be identified. All communications

and documents relevant to participants in the study will identify each person by the participant's study number only.

The electronic data will be used and stored in a secured and safe manner (antivirus software, firewall, password protected system, use of virtual private network (VPN)), and organizational arrangements are made (access control, paper files stored in locked cabinets, back-up and disaster recovery in place).

14.6 e-CRFs

The e-CRFs will be prepared by Medrio. The Investigator or authorized designee will be responsible for the timeliness, completeness and accuracy of all observations and other data pertinent to the clinical investigation in the e-CRF.

A e-CRF will be completed for each participant on inclusion in this protocol. The Investigator will make these forms available for thorough review and collection by the designated monitor at each scheduled monitoring visit.

Information collected in various source documents will be reported into the e-CRF and a 100% check of the consistency between the reported information (data, comments, etc.) and the source documents will be done. This check will be formally documented.

14.7 Protocol amendment

The Principal Investigator will ensure that the study protocol is strictly adhered to throughout, and that all data are collected and recorded correctly on the e-CRF. The Principal Investigator may contact the medical manager for a protocol waiver for minor deviations from the protocol *e.g*. healthy adult participant unable to attend during visit window.

All protocol modifications must be documented in writing. Any protocol amendment must be approved and signed by the Sponsor and the Principal Investigator and is to be submitted to the appropriate IEC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval by IEC (and Regulatory Authority, if applicable) must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial healthy participants, or when the change involves only logistical or administrative aspects of the study (*e.g*. change in clinical monitor(s), change of telephone number(s)).

The protocol amendment can be initiated by either Sponsor or by any Principal Investigator.

The Investigator will provide in writing the reasons for the proposed amendment and will discuss with the Sponsor.

14.8 Study monitoring

The monitoring will be performed by Sponsor monitor which is responsible for establishing the schedule and procedures to be followed for monitoring this study. On-site visits will be made prior to study initiation and at regular intervals during the study. Communications by telephone, telefax or mail may be used as needed to supplement site visits. Prior to the beginning of this study, the Investigator will be informed as to the anticipated frequency of the monitoring visits. In addition, the Investigator will receive reasonable notification prior to each monitoring visit during the course of the study.

The purpose of these visits is to verify:

- Adherence to the protocol,

- Completeness and accuracy of the e-CRFs, forms/documents sent to DNDi PV and study related source document.

Protocol deviations will also be identified and recorded on a "Protocol Deviation Log". At each visit, the Investigator will be expected to cooperate with the monitor for the review and verification of all e-CRFs, the study drug supply and inventory records and any additional records as may have been previously arranged.

14.8.1 Pre-study visit

At the pre-study visit, the study monitor will check that the Investigator has the technical means and the staff to carry out the study with regards to availability, participant recruitment, facilities and environment.

14.8.2 Study initiation

Prior to the start of the study, the Sponsor study manager will ensure that he or she has received the following information:

- Study protocol and financial agreement signed by all parts,
- Written statement of the IEC approval,
- Curriculum vitae of the Investigator.

14.8.3 Study monitoring visits

During the study, adherence to the protocol, conformity of the data entered in the e-CRF with the source documents will be checked at appropriate intervals by the study monitor.

14.8.4 Study termination visit

At the end of the study, the Sponsor study manager will ensure he has received:

- The completed e-CRFs,
- All unused medications and remaining packaging.

15 QUALITY ASSURANCE

15.1 Quality assurance program

Within the framework of the Quality Assurance system in place at CRW, the SOPs relative to the organization, realization, data collection, documents management and clinical studies verification ensure the ethical, scientific and technical quality of the trials.

An independent examination of the trial related activities and documents to determine whether the evaluated trial related activities are conducted, and the data recorded, analysed and accurately reported according to the protocol and to the current rules and regulations may be performed by the Sponsor or the CWR Quality Assurance Unit. The Investigator should make available for direct access all requested trial-related documents.

15.2 Good clinical practices

This trial will be conducted in adherence to the Malaysian Guideline for Good Clinical Practice, GCP as defined in the ICH E6 and other applicable regulatory requirements.

15.3 SOPs

Unless otherwise specified, all procedures mentioned in this protocol are the subject of detailed and referenced SOPs.

16 REPORTING AND PUBLICATIONS OF RESULTS

All clinical trials will be registered with a recognised clinical trial registry such as www.clinicaltrials.gov and in National Medical Research Register (NMRR, https://nmrr.gov.my/).

The final clinical study report (CSR) will be written in English as a Word format and its structure will follow PhinC Development template based upon the ICH E3[9], guidelines unless otherwise specified by the Sponsor during clinical trial agreement.

CSR has to be submitted to IRB and Regulatory.

All information concerning this study and the Sponsor's operation, such as patent applications, formulae, manufacturing processes, basic scientific data and formulation information supplied by the Sponsor and not previously published are considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent from the Sponsor or it designee.

It is understood by the Investigator that the information from the clinical study will be used by the Sponsor in connection with the development of acoziborole and, therefore, may be disclosed as required to other clinical Investigators or to government agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study.

Study drugs, the information in this document and in any future information supplied by the Sponsor contain trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations, should it be the case, the Sponsor will be informed in advance of this requirement.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

17 ARCHIVING OF DATA

The Investigator must ensure that all records pertaining to the conduct of the clinical study, ICFs, drug accountability records, source documents, and any other study documentation are adequately maintained for a period of 25 years as contractually agreed upon between the Investigator and the Sponsor. The Investigator must not destroy any records associated with the study without receiving approval from the Sponsor in writing. The Investigator must promptly notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options. Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document. All e-CRF data entered by the

site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The Sponsor will retain the original e-CRF data and audit trail.

18 REFERENCE LIST

[1] Priotto 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: 56–64.

[2] Kansiime F, Adibaku S, Wamboga C, Idi F, Kato CD, Yamuah L, Vaillant M, Kioy D, Olliaro P, Matovu E. 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 Feb 22;11(1):105. doi: 10.1186/s13071-018-2634-x. PMID: 29471865; PMCID: PMC5824494.

[3] Wall, R. J., Rico, E., Lukac, I., Zuccotto, F., Elg, S., Gilbert, I. H., Freund, Y., Alley, M. R. K., Field, M. C., Wyllie, S.,Horn, D. 2018. Clinical and veterinary trypanocidal benzoxaboroles target CPSF3, In: Proc Natl Acad Sci U S A. 115(38): 9616-9621.doi: 10.1073/pnas.1807915115.

[4] Jacobs et al. SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 Human African Trypanosomiasis. PLoS Negl Trop Dis 2011; 5 (6): e1151.

[5] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

[6] Treijtel et al. A cocktail interaction study evaluating the drug-drug interaction potential of the perpetrator drug ASP8477 at multiple ascending dose levels. Clin Pharmacol Drug Dev. 2019; 8(4): 529-540. doi: 10.1002/cpdd.660.

[7] Paulson et al. The pharmacokinetics of the CYP3A substrate midazolam after steady-state dosing of delafloxacin. Clin Ther 2017; 39(6): 1182-1190. doi: 10.1016/j.clinthera.2017.04.009.

[8] Guideline for Good Clinical Practice - ICH harmonised tripartite guideline Topic 6. January 1997. *Current version*.

[9] Guideline for Industry, ICH harmonised tripartite guideline Topic E3: Structure and Content of Clinical Study Reports. July 1996.