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:

[redacted]

Clinical study centre:

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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).