

**A PHASE 1, SINGLE-CENTER, REPEAT-DOSE, OPEN-LABEL,  
FIXED-SEQUENCE DRUG-DRUG INTERACTION STUDY OF  
ZX008 IN HEALTHY MALE OR FEMALE STUDY  
PARTICIPANTS 18 TO 55 YEARS OF AGE**

**PROTOCOL UP0132**

**PHASE 1**

**SHORT TITLE:**

Multiple-dose, Open-label, Drug-drug Interaction Study of ZX008

|                  |                 |
|------------------|-----------------|
| EudraCT Number:  | Not applicable. |
| EU Trial Number: | Not applicable. |
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| IDE Number:      | Not applicable. |
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## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Not applicable.

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## SERIOUS ADVERSE EVENT REPORTING

| Serious adverse event reporting (24 hours) |                                                                     |
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## SAFETY REPORTING OF ADVERSE EVENTS (SERIOUS)

| Safety reporting of adverse events (24h) |                               |
|------------------------------------------|-------------------------------|
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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

### Protocol title:

A Phase 1, Single-Center, Repeat-Dose, Open-Label, Fixed-Sequence Drug-Drug Interaction Study of ZX008 in Healthy Male or Female Study Participants 18 to 55 Years of Age.

### Short title:

Multiple-dose, Open-label, Drug-drug Interaction Study of ZX008

### Rationale:

ZX008 (fenfluramine hydrochloride 2.5mg/mL oral solution) is therapeutically useful in the treatment of highly refractory seizure disorders that may require multiple anti-epileptic medications. Results from in vitro studies have indicated that fenfluramine may induce cytochrome P450 (CYP)2B6 and CYP3A4, and its major metabolite norfenfluramine may inhibit multidrug and toxin extrusion protein 1 (MATE1). The study aims to determine the potential effect of fenfluramine and norfenfluramine following repeat doses of ZX008 on induction of CYP2B6 and CYP3A4 and inhibition of MATE1. Safety and tolerability of the probe drugs and ZX008 will be evaluated.

### Key Objectives and Endpoints

| Objectives                                                                                                                                                                                                                            | Endpoints/Estimands                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b>                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>To evaluate the single-dose PK of 3 probe drugs (midazolam as CYP3A4 substrate, bupropion as CYP2B6 substrate, metformin as MATE1 substrate) before and after repeat doses of ZX008</li> </ul> | <p>The following primary noncompartmental PK endpoints will be compared for the probe drugs after a single dose administered alone (Day 1) and following 17 days of ZX008 administration (Day 22):</p> <ul style="list-style-type: none"> <li><math>C_{max}</math> - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> <li>AUC - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> <li>AUC(0-t) - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> </ul> <p>with “predose” and “postdose” referring to administration of the probe drugs.</p> |
| <b>Secondary</b>                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of concomitant</li> </ul>                                                                                                                              | <ul style="list-style-type: none"> <li>Occurrence of TEAEs - Time Frame: Day 1 to 116</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

|                                                                                                                                                                                                                        |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <p>administration of the cocktail of probe drugs with ZX008 compared with the probe drugs alone</p> <ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of repeat doses of ZX008</li> </ul> |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

AUC=area under the concentration-time curve from 0 to infinity; AUC(0-t)=area under the curve from 0 to the time of the last quantifiable concentration;  $C_{max}$ =maximum concentration; CYP=cytochrome P450; MATE1=multidrug and toxin extrusion protein 1; PK=pharmacokinetic(s); TEAE=treatment-emergent adverse event; ZX008=fenfluramine hydrochloride

## Overall design

UP0132 is a Phase 1, single-center, repeat-dose, open-label, fixed-sequence drug-drug interaction study of ZX008 in 22 healthy male or female study participants aged 18 to 55 years. The study aims to determine the effect of fenfluramine and norfenfluramine on induction of CYP2B6 and CYP3A4 and inhibition of MATE1 following repeat doses of ZX008. Safety and tolerability of the probe drugs and ZX008 will be evaluated.

A sample for genotyping of CYP2B6 and CYP3A4 will be collected at Screening. Participants who are otherwise qualified but elect to not provide consent for genotyping are not eligible to participate in the study. Participants determined to have a poor metabolizer phenotype for CYP2B6 or CYP3A4 will be excluded from the study.

Eligible participants will report to the site on Day -1 (1 day before administration of the cocktail of probe drugs in Treatment Period 1) and will be housed in the site until discharge from the site on Day 26. Participants will fast overnight for at least 8 hours before and 4 hours after probe drug administration on study Days 1 and 22. All participants will receive standard meals for breakfast, lunch, and dinner at all other times.

Each participant will receive the following treatments:

- Treatment Period 1 - a single dose of the cocktail of probe drugs on Day 1
- Treatment Period 2 - repeat oral doses of ZX008, 15mg bid) from Day 6 through Day 25 (morning dose only), and a single dose of the cocktail of probe drugs on Day 22

There will be a washout phase of 4 days (Day 2 to Day 5) between the single dose of the cocktail of probe drugs in Treatment Period 1 (Day 1) and the first dose of ZX008 in Treatment Period 2 (Day 6). Study participants will be discharged from the site on Day 26, approximately 24 hours after the final scheduled dose of ZX008 on Day 25, after the final scheduled assessment, or after early termination or withdrawal. Study participants will return to the site for a Safety Follow-Up Visit 90 days after discharge from the site, or after early termination or withdrawal.

Blood plasma and urine sampling for the determination of concentrations of probe drugs, relevant metabolites, fenfluramine, and norfenfluramine are scheduled as follows:

### Treatment Period 1

- Serial blood samples for the determination of the plasma concentrations of each probe drug, 1-hydroxymidazolam, and hydroxybupropion (or [S,S]-hydroxybupropion if an

enantioselective assay is utilized) will be drawn from each participant at predose and at multiple time points (up to 96 hours) postdose, for a total of 17 samples per participant.

- Urine will be collected from each participant for the determination of metformin up to 72 hours after the metformin dose on Day 1.

#### Treatment Period 2

- Serial blood samples for the determination of the plasma concentrations of each probe drug, 1-hydroxymidazolam, and hydroxybupropion (or [S,S]-hydroxybupropion if an enantioselective assay is utilized) will be drawn from each participant at predose and at multiple time points (up to 96 hours) postdose, for a total of 17 samples per participant.
- Blood samples for the determination of trough plasma concentrations of fenfluramine and norfenfluramine will be drawn from each participant before the morning dose of ZX008 on Days 19 to 23.
- Urine will be collected from each participant for the determination of metformin up to 72 hours after the metformin dose on Day 22.

Participants will be discharged on study Day 26 after collection of the 96-hour pharmacokinetic (PK) blood sample, approximately 24 hours after the administration of the final dose of ZX008 in Treatment Period 2, contingent on safety and judgment of the investigator and in conjunction with the Sponsor, if deemed appropriate, and will return to the site for the Safety Follow-Up Visit.

Safety and tolerability will be monitored throughout the study by monitoring adverse events, examination of safety laboratory parameters, vital signs (systolic blood pressure, diastolic blood pressure, body temperature, respiratory rate, and pulse rate), electrocardiograms, echocardiogram, and physical examinations.

#### Number of participants

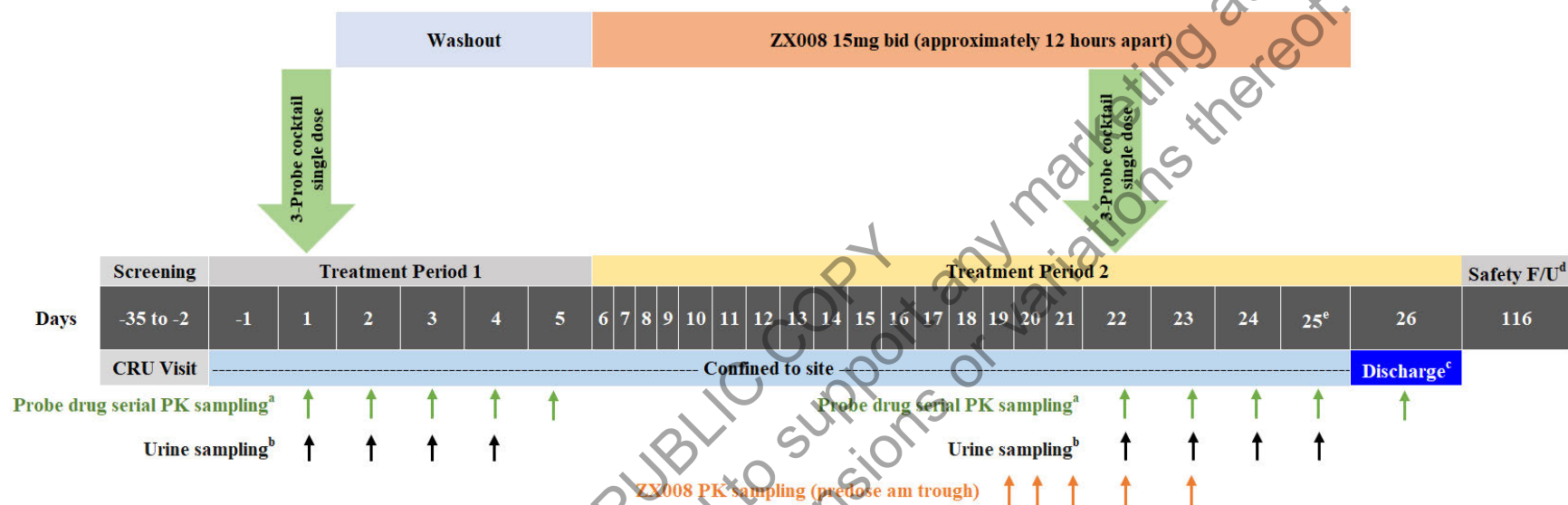
A sufficient number of study participants will be screened to ensure that 22 study participants enter Treatment Period 1 with the objective of having at least 18 study participants with reliable primary PK endpoints for both treatment periods.

#### Treatment groups and duration

Study participants will enter a Screening Period (up to 35 days before administration of the cocktail of probe drugs). All study participants will then progress through Treatment Period 1 and Treatment Period 2, comprising 6 days (Day -1 to Day 5) and 21 days (Day 6 to Day 26), respectively. Study participants will return to the site for a Safety Follow-Up Visit 90 days after discharge from the site, or after early termination or withdrawal.

## 1.2 Schema

Figure 1.1: Study schema



Abbreviations: F/U=follow-up; PK=pharmacokinetic; ZX008=fenfluramine hydrochloride.

a. Last sample drawn at 96 hours postdose (Day 5 or Day 26); see Schedule of Activities for full sampling schedule.

b. Urine will be collected in 6-hour intervals for metformin up to 36 hours, and then in 12-hour intervals up to 72 hours.

c. Participants discharged from the site on Day 26 (morning) after the 96-hour postdose PK sample if no safety concerns.

d. Participants will return to the site 90 days after discharge from the site or early termination to undergo an echocardiogram.

e. Morning dose of ZX008 15mg only.

### 1.3 Schedule of Activities

**Table 1.1: Schedule of Activities**

| Procedure/Assessments                                            | Screening Period               | Treatment Period 1             |   |                | Treatment Period 2 |    |    |                |    |    |                |    |    | Safety Follow-Up <sup>a</sup>       |
|------------------------------------------------------------------|--------------------------------|--------------------------------|---|----------------|--------------------|----|----|----------------|----|----|----------------|----|----|-------------------------------------|
| Day                                                              | -35 to -2                      | -1                             | 1 | 2 to 5         | 6 to 18            | 19 | 20 | 21             | 22 | 23 | 24             | 25 | 26 | 116<br>(or 90 days after discharge) |
| Informed consent form                                            | X                              |                                |   |                |                    |    |    |                |    |    |                |    |    |                                     |
| Verify inclusion/exclusion criteria                              | X                              | X                              | X |                |                    |    |    |                |    |    |                |    |    |                                     |
| Collect demographics                                             | X                              |                                |   |                |                    |    |    |                |    |    |                |    |    |                                     |
| Record information about habits and lifestyle required for study | X                              |                                |   |                |                    |    |    |                |    |    |                |    |    |                                     |
| Obtain medical, psychiatric, and surgical history                | X                              |                                |   |                |                    |    |    |                |    |    |                |    |    |                                     |
| Record prior and concomitant medications and procedures          | -----Throughout the study----- |                                |   |                |                    |    |    |                |    |    |                |    |    |                                     |
| Administer C-SSRS <sup>b</sup>                                   | X                              | X                              |   |                |                    |    |    |                |    |    |                |    | X  |                                     |
| Measure vital signs <sup>c</sup>                                 | X                              | X                              | X | X              | X                  |    |    |                | X  | X  |                |    | X  | X                                   |
| Perform a 12-lead ECG <sup>d</sup>                               | X                              | X                              | X | X              | X                  |    |    |                | X  | X  |                |    | X  | X                                   |
| Perform echocardiogram <sup>e</sup>                              | X                              |                                |   |                |                    |    |    |                |    |    |                |    | X  | X                                   |
| Measure height/weight (BMI)                                      | X                              |                                |   |                |                    |    |    |                |    |    |                |    |    |                                     |
| Perform physical examination <sup>f</sup>                        | X                              | -----Throughout the study----- |   |                |                    |    |    |                |    |    |                |    |    | X                                   |
| Labs for hematology, chemistry, and urinalysis <sup>g</sup>      | X                              | X                              |   | X <sup>h</sup> |                    |    |    | X <sup>h</sup> |    |    | X <sup>h</sup> |    | X  | X                                   |
| Obtain blood for viral serology (HIV-1/2Ab, HBsAg, HCV-Ab)       | X                              |                                |   |                |                    |    |    |                |    |    |                |    |    |                                     |

| Procedure/Assessments                                                                 | Screening Period | Treatment Period 1 |   |        | Treatment Period 2 |    |    |    |    |    |    |    |                |                                  | Safety Follow-Up <sup>a</sup> |
|---------------------------------------------------------------------------------------|------------------|--------------------|---|--------|--------------------|----|----|----|----|----|----|----|----------------|----------------------------------|-------------------------------|
| Day                                                                                   | -35 to -2        | -1                 | 1 | 2 to 5 | 6 to 18            | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26             | 116 (or 90 days after discharge) |                               |
| Obtain biological sample for CYP genotyping <sup>i</sup>                              | X                |                    |   |        |                    |    |    |    |    |    |    |    |                |                                  |                               |
| Obtain urine for drug screen                                                          | X                | X                  |   |        |                    |    |    |    |    |    |    |    |                |                                  |                               |
| Perform serum alcohol test                                                            | X                | X                  |   |        |                    |    |    |    |    |    |    |    |                |                                  |                               |
| Obtain blood for serum pregnancy test <sup>j</sup>                                    | X                |                    |   |        |                    |    |    |    |    |    |    |    |                |                                  |                               |
| Schedule check-in date/time to clinic                                                 | X                |                    |   |        |                    |    |    |    |    |    |    |    |                |                                  |                               |
| Check into clinic                                                                     |                  | X                  |   |        |                    |    |    |    |    |    |    |    |                |                                  |                               |
| Issue participant ID card for clinic                                                  | X <sup>k</sup>   |                    |   |        |                    |    |    |    |    |    |    |    |                |                                  |                               |
| Confinement to clinic                                                                 |                  | X                  | X | X      | X                  | X  | X  | X  | X  | X  | X  | X  | X <sup>l</sup> |                                  |                               |
| Obtain urine for pregnancy test <sup>j</sup>                                          |                  | X                  |   |        |                    |    |    |    |    |    |    |    | X              |                                  |                               |
| Administer probe drugs <sup>m</sup>                                                   |                  |                    | X |        |                    |    |    |    | X  |    |    |    |                |                                  |                               |
| Obtain blood samples for probe drugs PK <sup>n</sup>                                  |                  |                    | X | X      |                    |    |    |    | X  | X  | X  | X  | X              |                                  |                               |
| Obtain urine for metformin <sup>o</sup>                                               |                  |                    | X | X      |                    |    |    |    | X  | X  | X  | X  |                |                                  |                               |
| Administer ZX008 15mg bid <sup>p</sup>                                                |                  |                    |   |        | X                  | X  | X  | X  | X  | X  | X  | X  |                |                                  |                               |
| Drug accountability                                                                   |                  |                    | X |        | X                  | X  | X  | X  | X  | X  | X  | X  |                |                                  |                               |
| Obtain blood sample for trough level of fenfluramine and norfenfluramine <sup>q</sup> |                  |                    |   |        |                    | X  | X  | X  | X  | X  |    |    |                |                                  |                               |

| Procedure/Assessments           | Screening Period               | Treatment Period 1 |   |        | Treatment Period 2 |    |    |    |    |    |    |    |    | Safety Follow-Up <sup>a</sup>       |
|---------------------------------|--------------------------------|--------------------|---|--------|--------------------|----|----|----|----|----|----|----|----|-------------------------------------|
| Day                             | -35 to -2                      | -1                 | 1 | 2 to 5 | 6 to 18            | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 116<br>(or 90 days after discharge) |
| Record AEs                      | -----Throughout the study----- |                    |   |        |                    |    |    |    |    |    |    |    |    |                                     |
| Discharge participant from site |                                |                    |   |        |                    |    |    |    |    |    |    |    | X  |                                     |

AE=adverse event; BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-1/2Ab=human immunodeficiency virus 1 or 2 antibody; ICF=informed consent form; ID=identification; PK=pharmacokinetic(s); ZX008=fenfluramine hydrochloride

- a Day 116 ±10 days. Participants who prematurely discontinue from the study will be encouraged to undergo Safety Follow-up Visit procedures 90 days ±10 days after the final administration of ZX008.
- b At Screening, a full C-SSRS assessment (Screening/Baseline C-SSRS) will be performed. If the study participant has a positive response (“Yes”) to either Question 1, 2, 3, 4, or 5 of the C-SSRS assessments, this participant will be excluded. On Day -1 and Day 26, the “Since Last Visit” version of the questionnaire will be used.
- c Vital signs will be taken at Screening, Check-in (Day 1), Day 1 predose, Day 6 predose, and Day 22 predose. All predose vital signs will be taken within 30 minutes prior to dosing. After the administration of the cocktail of probe drugs or ZX008 (morning dose) on Day 1, Day 6, and Day 22, vital signs will be taken 5 hours (±15 minutes) postdose and 24 hours (±30 minutes) postdose (ie, Day 2, Day 7, and Day 23), at discharge from the site (Day 26), and at the Safety Follow-Up Visit.  
Vital signs will be taken in a semisupine position after 5 minutes of rest.  
A repeat set of blood pressure measurements will be allowed at Screening per investigator/designee.
- d Single 12-lead ECG recordings will be made at Screening, Check-in (Day -1), Day 1 predose, Day 6 predose, and Day 22 predose. After the administration of the cocktail of probe drugs or ZX008 (morning dose) on Day 1, Day 6, and Day 22, ECG recordings will be made 5 hours (±15 minutes) postdose and 24 hours (±30 minutes) postdose (ie, Day 2, Day 7, and Day 23), at discharge from the site (Day 26), and at the Safety Follow-Up Visit.  
ECG recordings will be made after the participant has been in the semisupine position for at least 5 minutes. All ECGs will be performed at the site and read locally by the investigator.  
In the case of clinically significant ECG findings (including QTcF >500msec, change from Baseline: QTcF >60msec), 2 additional ECGs will be performed. If they have the abnormality related to numerical measurements, then eligibility will be based on the average of triplicate ECG readings. If the abnormality does not relate to numerical measurements, eligibility will be based on clinical judgement.
- e All echocardiograms will be conducted on standard equipment and digitally transferred for central reading to the echocardiogram core laboratory.
- f At Screening and on Day 26: complete physical examination; from Day -1 through Day 25: as clinically indicated; at Safety Follow-Up Visit: brief physical examination.
- g Additionally, a coagulation test may be performed in case of liver toxicity.
- h Only on Day 5, on Day 21 predose, and on Day 24 predose.
- i Participants who do not provide consent for genotyping are not eligible to participate.
- j For women of childbearing potential only.

- 
- k The participant ID card should be provided to the study participant once they have signed the ICF and successfully completed all screening assessments. The ID card should be given to study participant before they leave the clinic (after Screening Visit).
- l Participants will be discharged the morning of Day 26 after completion of scheduled procedures contingent on safety and judgment of the investigator and in conjunction with the Sponsor, if deemed appropriate.
- m On Day 1 and Day 22, the probe drugs will be administered in the morning. The Day 22 dose of probe drugs will be administered at the same time as the morning dose of ZX008. Participants will fast for 8 hours before and 4 hours after the administration of the cocktail of probe drugs.
- n At predose, 0.25, 0.50, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours postdose in Treatment Periods 1 and 2.
- o Collected urine predose (within 2 hours), and postdose in 6-hour intervals up to 36 hours, and then in 12-hour intervals up to 72 hours in Treatment Periods 1 and 2.
- p ZX008 15mg will be administered twice daily (approximately 12 hours apart; one dose in the morning, one dose in the evening) starting on Day 6. On Day 25, only the morning dose will be administered.
- q Draw blood samples prior to (within 30 minutes) the morning dose of ZX008 on Days 19, 20, 21, 22, and 23 of Treatment Period 2.

## 2 INTRODUCTION

### 2.1 Study rationale

ZX008 (fenfluramine hydrochloride 2.5mg/mL oral solution) is therapeutically useful in the treatment of highly refractory seizure disorders that may require multiple anti-epileptic medications. Results from in vitro studies have indicated that fenfluramine may induce cytochrome P450 (CYP)2B6 and CYP3A4, and its major metabolite norfenfluramine may inhibit multidrug and toxin extrusion protein 1 (MATE1). The study aims to determine the potential effect of fenfluramine and norfenfluramine following repeat doses of ZX008 on induction of CYP2B6 and CYP3A4 and inhibition of MATE1. Safety and tolerability of the probe drugs and ZX008 will be evaluated.

### 2.2 Background

ZX008 has been approved in the US, EU, UK, and Japan for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older as well as for the treatment of seizures in patients 2 years of age and older with Lennox-Gastaut syndrome.

Results from in vitro studies have indicated that fenfluramine may induce CYP2B6 and CYP3A4, and norfenfluramine may inhibit MATE1. In vitro data from a preclinical study in cryopreserved human hepatocytes indicated that fenfluramine had little or no effect on CYP1A2 mRNA but evoked increases in CYP2B6 and CYP3A4 mRNA (XT153038). The observed increases in CYP3A4 mRNA levels were <20% of that mediated by the positive controls. Fenfluramine had little effect on CYP2B6 mRNA up to a test concentration of 10µM, but concentrations ≥20µM caused increases (>2-fold) in CYP2B6 mRNA levels in 2 of 3 hepatocyte cultures. Norfenfluramine did not induce any CYP mRNA more than ~20% of the control inducers. With fenfluramine, CYP2B6 mRNA in 1 of 3 donors was slightly >20% of the positive control; and for norfenfluramine, 2 of 3 donors showed slightly more than 20% of the positive control. Assessments with the mechanistic static model yielded R-values >0.8 (range 0.96 to 0.99), suggesting that induction of CYP2B6 was unlikely. An additional study was conducted in cryopreserved human hepatocytes to estimate relative induction score values and predict effects of fenfluramine and norfenfluramine on midazolam as a CYP3A4 index substrate (XTC20003). From this assessment, fenfluramine-mediated decreases in midazolam AUC were predicted to be 35.8%, 22.2%, and 6.59% in the 3 hepatocyte lots. Norfenfluramine was predicted to decrease midazolam AUC by 26.4%, 17.5%, and 3.21% in the 3 hepatocyte lots. The Food and Drug Administration guidance notes that a drug is considered to have induction potential if results in at least 1 donor exceeds the predefined 20% cutoff (or AUC ratio ≤0.8).

Fenfluramine and norfenfluramine inhibit MATE1 with IC<sub>50</sub> values of 9.02µM and 4.60µM, respectively, in transfected Human Embryonic Kidney 293 (HEK293) cells (XT168020). In vivo inhibition of MATE1 was considered unlikely as the IC<sub>50</sub> values are 56-fold and 49-fold higher than the respective unbound steady-state C<sub>max</sub> values at the maximum ZX008 dose (0.8mg/kg/day, with a maximum of 30mg/day) in Dravet syndrome patients.

Analysis of these preclinical data suggests that ZX008 is not anticipated to perpetrate a clinically meaningful effect on the pharmacokinetics (PK) of other drugs. However, at approval of the Marketing Authorisation Applications for ZX008 in Dravet syndrome, the European Medicines Agency (EMA) recommended postauthorization clinical studies to investigate whether (i) fenfluramine is an inducer of CYP2B6 (“at clinically relevant portal vein concentrations”) and

CYP3A4 (“at maximal intestinal concentrations”), and (ii) norfenfluramine is a clinically relevant inhibitor of MATE1 with the clinically relevant substrate metformin.

This study aims to determine whether ZX008 perpetrates the aforementioned drug-drug interactions (DDIs) following repeat-dose administration of clinically relevant doses of ZX008. The potential for the specified DDIs will be investigated using a cocktail of specific probe substrates (bupropion as a CYP2B6 substrate, midazolam as a CYP3A4 substrate, and metformin as a MATE1 substrate) to enable the simultaneous evaluation of multiple interactions with ZX008 in a single study. Safety and tolerability of the probe drugs and ZX008 will be evaluated.

### 2.3 Benefit/risk assessment

The participants enrolled in this study are not expected to receive medical benefits from participation.

All 3 probe drugs are approved therapeutics; additional details are provided in Section 4.3.2. The selected single dose of each probe drug in this study is less than (midazolam, bupropion) or equal to (metformin) the lowest indicated starting dose in the US. No new safety concerns are expected. Various combinations of 2 of these 3 drugs have been well tolerated when used as oral probe substrates in clinical DDI studies and support the tolerance of the proposed cocktail of probe drugs and its feasibility for the objectives of this study. No PK or major pharmacodynamic interactions are expected between the 3 probe drugs and ZX008.

Bupropion (a sensitive CYP2B6 substrate) and midazolam (a sensitive CYP3A substrate) are eliminated by different routes via distinct CYP enzymes. No direct PK interactions are expected when the two are administered together in the same DDI study. Study participants will be housed in a Phase 1 clinical research unit (referred to as the “site” in this document) for the duration of the study. The risks of using this cocktail of probe drugs at the proposed doses in healthy adults in a controlled Phase 1 clinical research unit are expected to be low by minimizing systemic exposures without compromising study outcomes. The use of low doses of midazolam and bupropion in the study are expected to minimize the potential for pharmacodynamic interactions between the two, mainly sedation. The well-characterized “Geneva cocktail” includes oral midazolam (1mg, as a CYP3A4 substrate) and oral bupropion (25mg, as a CYP2B6 substrate) amongst a mixture of 6 drugs (Bosilkovska, 2014). A single oral dose of 2mg midazolam with 75mg bupropion has been used to evaluate the CYP induction effect of lemborexant (Landry, 2021). Oral midazolam (2mg) is a component of the well-studied 6-probe “Basel cocktail” used for DDI studies and CYP phenotyping (Derungs, 2016). Midazolam (5mg) and metformin (1000mg, a MATE1/2-K substrate) have been administered together orally as probe substrates in clinical DDI studies and are well tolerated (Li, 2022). Although endogenous substrates have been identified as markers to evaluate in vivo MATE1-based interactions (Ito, 2012; Miyake, 2021), this study proposes to use metformin as the probe substrate to adhere to the specific postapproval recommendation by EMA. Metformin has no clinically relevant perpetrator effects on the PK of over 40 coadministered drugs (Hachad, 2010). Metformin is not metabolized and is excreted unchanged in the urine.

Repeat doses of ZX008 15mg bid (30mg/day) and 60mg bid (120mg/day) have been shown to be well tolerated in healthy adult male and female participants in the development program. The most commonly reported adverse reactions of ZX008 are decreased appetite, diarrhoea, echocardiogram abnormal, fatigue, pyrexia, blood glucose decreased, and somnolence. More

detailed information about the known and expected risks as well as reasonably expected AEs of ZX008 may be found in the Investigator's Brochure and current United States Prescribing Information (USPI, 2023).

Overall, the risks of administering the proposed cocktail of probe drugs with ZX008 in a Phase 1 clinical research unit in healthy young adults are expected to be acceptable and will provide necessary information for the ZX008 program while fulfilling the regulatory recommendations.

Additional risks in the study may include:

- Participants may experience temporary discomfort, bruising, local swelling, and/or, in rare circumstances, infection at the needle site during cannulation for blood sampling.
- Stickers used to secure electrocardiogram (ECG) electrode pads on parts of the body such as chest, arms, and legs may cause skin irritation, and slight discomfort or bruising may occur when the electrode pads are attached and/or removed.

### 3 OBJECTIVES AND ENDPOINTS

| Objectives                                                                                                                                                                                                                                                                          | Endpoints/Estimands                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b>                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <ul style="list-style-type: none"> <li>• To evaluate the single-dose PK of 3 probe drugs (midazolam as CYP3A4 substrate, bupropion as CYP2B6 substrate, metformin as MATE1 substrate) before and after repeat doses of ZX008</li> </ul>                                             | <p>The following primary noncompartmental PK endpoints will be compared for the probe drugs after a single dose administered alone (Day 1) and following 17 days of ZX008 administration (Day 22):</p> <ul style="list-style-type: none"> <li>• <math>C_{max}</math> - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> <li>• AUC - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> <li>• AUC(0-t) - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> </ul> <p>with "predose" and "postdose" referring to administration of the probe drugs.</p> |
| <b>Secondary</b>                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <ul style="list-style-type: none"> <li>• To evaluate the safety and tolerability of concomitant administration of the cocktail of probe drugs with ZX008 compared with the probe drugs alone</li> <li>• To evaluate the safety and tolerability of repeat doses of ZX008</li> </ul> | <ul style="list-style-type: none"> <li>• Occurrence of TEAEs - Time Frame: Day 1 to 116</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| <b>Tertiary/Exploratory</b>                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>To evaluate the effect of repeat doses of ZX008 15mg bid on single-dose PK of the probe drugs</li> </ul>                                                                     | <p>The following noncompartmental PK endpoints will be estimated for the probe drugs administered alone (Day 1) and following 17 days of ZX008 administration (Day 22):</p> <ul style="list-style-type: none"> <li><math>t_{max}</math>, <math>C_{last}</math>, <math>t_{last}</math>, <math>CL/F</math>, <math>V_z/F</math>, <math>\lambda_z</math>, and <math>t_{1/2}</math> - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> <li><math>f_e</math> and <math>A_e</math> of metformin - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> <li><math>CL_R</math> of metformin when administered alone and following 17 days of ZX008 administration - Time Frame: predose and at multiple time points (up to 72 hours) postdose</li> </ul> <p>with “predose” and “postdose” referring to administration of the probe drugs.</p> |
| <ul style="list-style-type: none"> <li>To evaluate the effect of repeat doses of ZX008 15mg bid on single-dose PK of the probe drug metabolites</li> </ul>                                                          | <p>The following noncompartmental PK endpoints will be estimated for the metabolites (1-hydroxymidazolam and hydroxybupropion [or [S,S]-hydroxybupropion if an enantioselective assay is selected]) when the probe drugs are administered alone (Day1) and following 17 days of ZX008 administration (Day 22):</p> <ul style="list-style-type: none"> <li><math>C_{max}</math>, <math>AUC(0-t)</math>, <math>AUC</math>, <math>t_{max}</math>, <math>C_{last}</math>, <math>t_{last}</math>, <math>\lambda_z</math>, and <math>t_{1/2}</math> - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> <li>Metabolite to parent ratio for <math>C_{max}</math>, <math>AUC(0-t)</math>, and <math>AUC</math> - Time Frame: predose and at multiple time points (up to 96 hours) postdose</li> </ul>                                                                   |
| <ul style="list-style-type: none"> <li>To evaluate plasma concentrations of fenfluramine and norfenfluramine after repeat doses of ZX008</li> </ul>                                                                 | <ul style="list-style-type: none"> <li>Trough (predose) plasma concentrations of fenfluramine and norfenfluramine - Time Frame: Day 19 to 23</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"> <li>To evaluate other measures of safety and tolerability of a single oral dose of the cocktail of probe drugs, repeat doses of ZX008 alone and in combination with a</li> </ul> | <ul style="list-style-type: none"> <li>Changes from Baseline in vital signs (pulse rate, respiratory rate, SBP, DBP, and temperature) - Time Frame: Day -35 to 116</li> <li>Physical examination findings - Time Frame: Day -35 to 116</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| single oral dose of the cocktail of probe drugs | <ul style="list-style-type: none"> <li>12-lead ECG results and findings - Time Frame: Day -35 to 116</li> <li>Occurrence of clinically significant abnormal valve regurgitation and/or increased pulmonary arterial pressure - Time Frame: Day -35 to 116</li> <li>Changes from Baseline in clinical laboratory test results (hematology, clinical chemistry, and urinalysis) - Time Frame: Day -35 to 116</li> <li>Assessment of suicidality using C-SSRS - Time Frame: Screening and on Day -1, and Day 26</li> </ul> |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Ae=cumulative amount of unchanged drug excreted in urine; AUC=area under the curve from 0 to infinity; AUC(0-t)=area under the curve from 0 to the time of the last quantifiable concentration; CL/F=apparent total body clearance; CL<sub>R</sub>=renal clearance; C<sub>last</sub>=last observed (quantifiable) concentration; C<sub>max</sub>=maximum concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; DBP=diastolic blood pressure; ECG=electrocardiogram; fe=fraction of the dose excreted unchanged in urine; MATE1=multidrug and toxin extrusion protein 1; PK=pharmacokinetic(s); t<sub>1/2</sub>=terminal elimination half-life; SBP=systolic blood pressure; TEAE=treatment-emergent adverse event; t<sub>last</sub>=time of C<sub>last</sub>; t<sub>max</sub>=time of C<sub>max</sub>; V<sub>Z</sub>/F=apparent volume of distribution; ZX008=fenfluramine hydrochloride; λ<sub>z</sub>=first order terminal elimination rate constant

## 4 STUDY DESIGN

### 4.1 Overall design

UP0132 is a Phase 1, single-center, repeat-dose, open-label, fixed-sequence DDI study of ZX008 in 22 healthy male or female study participants aged 18 to 55 years. The study aims to determine the effect of fenfluramine and norfenfluramine following repeat doses of ZX008 on induction of CYP2B6 and CYP3A4 and inhibition of MATE1. Safety and tolerability of the probe drugs and ZX008 will be evaluated.

A sufficient number of study participants will be screened to ensure that 22 study participants enter Treatment Period 1 with the objective of having at least 18 study participants with reliable primary PK endpoints for both treatment periods. Study participants will enter a Screening Period (up to 35 days before administration of the probe drugs). All study participants will then progress through Treatment Period 1 and Treatment Period 2, comprising 6 days (Day -1 to Day 5) and 21 days (Day 6 to Day 26), respectively.

A blood sample will be collected at Screening and will be used for genotyping of CYP2B6 and CYP3A4. Participants who are otherwise qualified but elect to not provide consent for genotyping are not eligible to participate in the study. Participants determined to have a poor metabolizer phenotype for CYP2B6 or CYP3A4 will be excluded from the study.

Eligible participants will report to the site on Day -1 (1 day before administration of the cocktail of probe drugs in Treatment Period 1) and will be housed at the site until discharge from the site on Day 26, approximately 24 hours after the final scheduled dose of ZX008 on Day 25, or after the final scheduled assessment. Participants will fast overnight for at least 8 hours before and 4 hours after probe drug administration on study Days 1 and 22. All participants will receive standard meals for breakfast, lunch, and dinner at all other times.

Each participant will receive the following treatments:

- Treatment Period 1 – a single dose of the cocktail of probe drugs on Day 1
- Treatment Period 2 – repeat oral doses of ZX008 (15mg bid) from Day 6 through Day 25 (morning dose only), and a single dose of the cocktail of probe drugs on Day 22

There will be a washout phase of 4 days (Day 2 to Day 5) between the single dose of the cocktail of probe drugs in Treatment Period 1 (Day 1) and the first dose of ZX008 in Treatment Period 2 (Day 6). Study participants will be discharged from the site 24 hours after the final planned dose of ZX008 is given on Day 25, or after early termination or withdrawal. Study participants will return to the site for a Safety Follow-Up Visit 90 days after from the site, or after early termination or withdrawal.

Blood plasma and urine sampling for the determination of concentrations of probe drugs, relevant metabolites, fenfluramine, and norfenfluramine are scheduled as follows:

#### Treatment Period 1

- Serial blood samples for the determination of the plasma concentrations of each probe drug, 1-hydroxymidazolam, and hydroxybupropion (or [S,S]-hydroxybupropion if an enantioselective assay is utilized) will be drawn from each participant at predose, 0.25, 0.50, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours postdose, for a total of 17 samples per participant.
- Urine will be collected from each participant for the determination of metformin in 6-hour intervals up to 36 hours, and then in 12-hour intervals up to 72 hours after the metformin dose on Day 1.

#### Treatment Period 2

- Serial blood samples for the determination of the plasma concentrations of each probe drug, 1-hydroxymidazolam, and hydroxybupropion (or [S,S]-hydroxybupropion if an enantioselective assay is utilized) will be drawn from each participant at predose, 0.25, 0.50, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours postdose, for a total of 17 samples per participant.
- Blood samples for the determination of trough plasma concentrations of fenfluramine and norfenfluramine will be drawn from each participant before the morning dose of ZX008 on Days 19 to 23.
- Urine will be collected from each participant for the determination of metformin in 6-hour intervals up to 36 hours, and then in 12-hour intervals up to 72 hours after the metformin dose on Day 22.

The proposed plasma and urine sampling scheme are derived from literature information for similar dosing regimens and expected to capture the PK profiles (AUC) of each probe drug and the relevant metabolites.

Participants will be discharged on Day 26 after collection of the 96-hour PK blood sample, approximately 24 hours after the administration of the final dose of ZX008 in Treatment Period 2, contingent on safety and judgment of the investigator and in conjunction with the Sponsor, if deemed appropriate.

Safety and tolerability will be monitored throughout the study by AEs, examination of safety laboratory parameters, vital signs (SBP, DBP, body temperature, respiratory rate, and pulse rate), ECGs, echocardiogram (ECHO), and physical examinations as noted in [Table 1.1](#).

## 4.2 Scientific rationale for study design

This study aims to determine the effect of fenfluramine and norfenfluramine following repeat doses of ZX008 on induction of CYP2B6 and CYP3A4 and inhibition of MATE1 in healthy adult male and female participants by comparing the PK of probe drugs when administered alone (Day 1) versus after repeat doses of ZX008 (Day 22). Administration of the object substrates in a cocktail allows the simultaneous evaluation of multiple interactions with ZX008 as the potential perpetrator in a single study. Safety and tolerability of the probe drugs and ZX008 will be evaluated.

The design is standard and is considered adequate to meet the objectives of the study. The dosing and PK sampling schedules are considered appropriate based on the information available in the ZX008 development program and literature (for probe drugs). The safety assessments for the study are accepted measures for ensuring the safety of participants during a clinical study. The rationale for dose selection and duration of the treatment is discussed in [Section 4.3](#).

## 4.3 Justification for dose

### 4.3.1 ZX008

The approved dose of ZX008 in patients with Dravet syndrome or Lennox-Gastaut syndrome is 0.2 to 0.8mg/kg/day in 2 equally divided doses, with a maximum total daily dose of 30mg (20mg/day with concomitant stiripentol). As noted above, repeat doses of ZX008 up to 60mg bid (120mg/day) have been well tolerated by healthy adult male and female participants. A repeat-dose regimen of 15mg bid ZX008 for a duration of 17 days has been selected because it represents the maximum approved daily dose and is expected to provide maximal intestinal concentrations with clinically relevant portal vein concentrations as indicated in the EMA postauthorization study recommendations. About 17 days of ZX008 dosing is considered adequate for maximal in vivo induction of CYP2B6 and CYP3A4 mediated by pregnane X receptor (PXR) and constitutive androstane receptor (CAR) pathways. Administration of ZX008 alone will continue on Days 23 to 25 to ensure that any potential effect of ZX008 on the probe drug clearance will be sustained during washout of the probe drugs.

### 4.3.2 Probe drugs

Concomitant administration of a cocktail or mixture of probe drugs allows more than one interaction to be tested simultaneously in the same study and in the same group of participants. The probe drugs in this study have been specifically selected to evaluate the activity of CYP2B6, CYP3A4, and MATE1 and the potential impact of repeat doses of ZX008 on their PK.

The probe drug cocktail consists of metformin, midazolam, and bupropion. All 3 probe drugs will be administered orally as a single dose of the immediate release (IR) formulations in each treatment period. The probe drugs are described below:

1. Metformin is not metabolized and is recommended as a clinical marker substrate of MATE1, MATE2-K, and OCT2 transporters (ICH, 2022). Following a single oral administration,  $t_{1/2}$  is approximately 6.5 hours (Glucophage USPI, 2018). The indicated starting dose of

metformin hydrochloride IR is 500mg orally bid, up to a maximum dose of 2550mg/day, given in divided doses. Metformin has no clinically relevant perpetrator effects on the PK of over 40 coadministered drugs (Hachad, 2010). A single oral dose of 500mg metformin hydrochloride will be evaluated in each treatment period to ensure adequate detection of urine concentrations.

2. Midazolam is exclusively metabolized in human liver and intestine by CYP3A4 to its active metabolite,  $\alpha$ -hydroxymidazolam (also termed 1-hydroxymidazolam), followed by glucuronidation of the  $\alpha$ -hydroxyl metabolite which is present in unconjugated and conjugated forms in human plasma (Heizmann, 1983; Midazolam Syrup USPI, 2012). Midazolam hydrochloride syrup is currently indicated for use as a single dose (0.25 to 1mg/kg with a maximum dose of 20mg) for preprocedural sedation and anxiolysis in pediatric patients. In adults, the usual dosage range for midazolam is 1 to 5mg given intravenously over a 2-minute period, and 0.07 to 0.08mg/kg intramuscularly (about 5mg for an average healthy adult) administered 30 to 60 minutes before a procedure. The absolute bioavailability of oral midazolam in adults is variable but low (32% to 61% at 10mg; Heizmann, 1983). Mean elimination  $t_{1/2}$  values of midazolam following single oral doses of 2 to 15mg midazolam hydrochloride range from 1.3 to 5.9 hours in healthy young adults; mean  $t_{1/2}$  values 1-hydroxymidazolam range from 1.2 to 10.3 hours. 1-hydroxymidazolam constitutes 63% to 80% of all biotransformation products, while 4-hydroxymidazolam and 1,4-dihydroxymidazolam are minor metabolites ( $\leq 5\%$ ) (Midazolam Syrup USPI, 2012). The 1-hydroxymidazolam glucuronide is the principal moiety excreted in urine; smaller amounts of glucuronidated 4-hydroxymidazolam and dihydroxymidazolam are also excreted in urine. Orally administered midazolam is an accepted in vivo probe substrate for CYP3A4/5 in DDI assessments (EMA, Guideline on the Investigation of Drug Interactions, 2012; ICH, Guideline M12 on drug interaction studies, Step 2b, 2022). Inducers such as rifampicin can also induce UDP-glycosyltransferases via PXR resulting in altered exposures to 1-hydroxymidazolam (Link, 2008). Hence, bioanalysis of total 1-hydroxymidazolam concentrations may be necessary to adequately reflect induction of CYP3A4 activity (Derungs, 2016). A single 2mg dose of oral midazolam will be evaluated in each treatment period of this study.
3. Bupropion is highly metabolized to its active metabolites by 3 different routes: hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Bupropion is considered to be a sensitive index substrate of CYP2B6 (defined as subject to an increase in AUC of  $\geq 5$ -fold with strong index inhibitors) (European Medicines Agency, Guideline on the Investigation of Drug Interactions, 2012; International Conference on Harmonisation, Guideline M12 on drug interaction studies, Step 2b, 2022). The indicated starting dose of bupropion IR is 200mg/day given as 100mg bid, with a maximum dose of 450mg/day given as 150mg tid. Racemic bupropion and hydroxybupropion both have a mean elimination  $t_{1/2}$  of 20 hours (Wellbutrin USPI); mean values ranging from 8.1 to 34.6 hours have been reported in the literature. Following a single oral dose of 100mg racemic bupropion IR, mean elimination  $t_{1/2}$  of S-bupropion and [S,S]-hydroxybupropion is 7.2 and 14.6 hours, respectively (Masters, 2016); mean  $t_{1/2}$  values in the range of 7.2 to 34.6 hours and 10.8 to 43.1 hours for S-bupropion and [S,S]-hydroxybupropion, respectively, have also been reported following single oral doses of racemic bupropion IR. The formation of hydroxybupropion is primarily mediated by hepatic CYP2B6; no other CYPs are involved in

the formation of the other metabolites. Hydroxybupropion is further glucuronidated. Analyses of plasma concentrations of racemic bupropion and its enantiomers following induction of CYP2B6 by rifampin or ritonavir have shown that exposures to racemic bupropion and S-bupropion decrease comparably (Kharasch, 2008a; Kharasch, 2008b). Both bupropion and hydroxybupropion (or their enantiomers) are often analyzed in clinical DDI studies to evaluate inhibition or induction of CYP2B6 (Landry, 2021). In the presence of a CYP2B6 inducer, the formation and elimination rates for hydroxybupropion are both altered; hydroxybupropion is more rapidly generated by the higher rate of bupropion metabolism. At the same time, sequential glucuronidation of hydroxybupropion by UDP-glycosyltransferases can also be induced via PXR-CAR regulation. Therefore, both formation and elimination rates for hydroxybupropion may increase with CYP2B6 induction. A single oral dose of 75mg racemic bupropion hydrochloride will be evaluated in each treatment period in this study. The low dose of bupropion is not likely to meaningfully affect exposures to fenfluramine and norfenfluramine already at steady state.

#### **4.4 End of study definition**

A participant is considered to have completed the study if he/she has completed all periods of the study including the Safety Follow-Up Visit on Day 116. Participants who prematurely discontinue from the study must undergo Safety Follow-Up Visit procedures 90 days after the final administration of ZX008.

The global end of the study is defined as the date of the last visit of the last participant in the study.

### **5 STUDY POPULATION**

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

#### **5.1 Inclusion criteria**

Participants are eligible to be included in the study only if all of the following criteria apply:

##### **Age**

1. Participant must be 18 to 55 years of age inclusive at the time of signing the informed consent form (ICF).

##### **Type of participant and disease characteristics**

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Participants who have normal renal function ( $\geq 60$  mL/min estimated glomerular filtration rate by CKD-EPI equation).

##### **Weight**

4. Body weight of at least 50kg and body mass index within the range 18 to 32kg/m<sup>2</sup> (inclusive).

##### **Sex**

5. Male or female

- A male participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol starting from Screening through at least 5 terminal half-lives (approximately 7 days) after the final dose of ZX008 and refrain from donating sperm during this period.
- A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:

Not a woman of childbearing potential (WOCBP) as defined in Appendix 4  
OR

A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 5 terminal half-lives (approximately 7 days), corresponding to time needed to eliminate study treatment after the final dose of ZX008.

## Informed consent

6. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

## 5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

### Medical conditions

1. Participant has any medical or psychiatric condition including previous or current episode of suicidal ideation that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Participant has a history or clinical manifestations of a significant neurological, renal, gastrointestinal, pulmonary, hematologic, immunologic, or psychiatric disease that would preclude study participation, as judged by the investigator.
3. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) above 1.1x upper limit of normal (ULN).
4. Bilirubin >ULN (isolated bilirubin <1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
5. Participant has clinically significant current or past history of cardiovascular or cerebrovascular disease, such as valvular heart disease, and/or pulmonary hypertension. Participants with any history of stroke or myocardial infarction are excluded.
6. Clinically significant history or presence of ECG or ECHO findings as judged by the investigator or designee at the Screening Visit and Check-in, including each criterion listed below:
  - Abnormal sinus rhythm (heart rate outside of 40bpm and 100bpm)
  - QTcF interval >450msec for male participants or >470msec for female participants (QTcF is the QT interval corrected for heart rate according to Fridericia's formula, it can be either machine read or manually overread)
  - QRS interval >120msec, confirmed by manual over read

- PR interval >220msec
  - Greater than trace aortic valve regurgitation
  - Greater than trace mitral valve regurgitation
  - Possible signs of pulmonary arterial hypertension (PAH) with abnormal pulmonary artery systolic pressure (PASP) or PASP >35mmHg
  - Evidence of left ventricular dysfunction (systolic or diastolic)
  - Clinically significant structural cardiac abnormality, including, but not limited to, mitral valve prolapse, atrial or ventricular septal defects, and patent ductus arteriosus with reversal of shunt (right to left shunt). Note: Patent foramen ovale or a bicuspid aortic valve is not considered exclusionary
7. Clinically significant abnormal blood pressure (as determined by the investigator).
  8. Participant has a current or past history of glaucoma.
  9. Participant has a current history of alcohol or drug use disorder, or previously diagnosed with an eating disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders V, within the previous 12 months.
  10. Participant is unable or unwilling to abstain from alcohol from 72 hours prior to the administration of study treatments until discharge.
  11. [REDACTED]  
[REDACTED]  
as indicated by a positive response (“Yes”) to either Question 1, 2, 3, 4, or 5 of the “Screening/Baseline” version of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the Screening Visit, or has a positive response (“Yes”) on any item of the Suicidal Behavior section, except for the [REDACTED]  
[REDACTED]
  12. Participant has a known hypersensitivity to any components of ZX008 or the probe drugs (metformin, midazolam, and bupropion drug products).

#### **Prior/Concomitant therapy**

13. Participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin) within 30 days before the first administration of the cocktail of 3 probe drugs (metformin, midazolam, bupropion) and through the day of discharge from the site.
14. Participant has used other prescription drugs, including vaccinations, over-the-counter medications, herbal/traditional medicines, or dietary supplements within 14 days before the first administration of the cocktail of probe drugs (excluding medicines for external use), with the exception of acetaminophen (up to 2g/day).

#### **Prior/Concurrent clinical study experience**

15. Participant has previously participated in this study or participant has previously been assigned to treatment in a study of ZX008.

16. Participant has participated in another study of an investigational medicinal product (IMP) (and/or an investigational device) within the previous 30 days or 5 terminal half-lives (whichever is longer) of the first dose of the cocktail of probe drugs in this study or is currently participating in another study of an IMP (and/or an investigational device).

### **Diagnostic assessments**

17. Consent to genotyping is required for participation in the study. Poor metabolizers of CYP3A4 or CYP2B6 based on genotyping and as categorized by the testing laboratory will be excluded from the study.
18. Positive test for alcohol and/or prohibited concomitant drugs (including cotinine) at Screening Visit and on Day -1.
19. Positive test result for hepatitis B surface antigen, hepatitis C virus antibody test, or human immunodeficiency virus (HIV) antibody test at Screening Visit.

### **Other exclusions**

20. Participant has donated blood or plasma or has experienced blood loss  $\geq 500\text{mL}$  within 90 days,  $\geq 200\text{mL}$  within 30 days, or has donated any blood or plasma within 14 days before first administration of study treatments.
21. Any consumption of food products with a known DDI impact (eg, grapefruit, grapefruit juice, Seville oranges, or products containing them) for at least 1 week before Day 1 and through day of discharge from the site.
22. Consumption of more than 600mg of caffeine/day (1 cup of coffee contains approximately 100mg of caffeine, 1 cup of tea approximately 30mg, and 1 glass of cola approximately 20mg) within 30 days before Day 1 and through day of discharge from the site.
23. Participant is a current smoker or has used nicotine-containing products (eg, tobacco, patches, gum, vapes, or e-cigarettes) within 35 days before Day 1 and through day of discharge from the site.
24. Participant is involved in strenuous activity or contact sports from Day -1 through day of discharge from the site.

## **5.3 Lifestyle restrictions**

### **5.3.1 Meals and dietary restrictions**

- Unless otherwise indicated, all doses of ZX008 in this study will be administered in the fed state. Breakfast and dinner will be served at 1 to 2 hours ( $\pm 10$  minutes) prior to the planned dosing time. The time of the start of the meal will be recorded. Participants will fast overnight for at least 8 hours prior to dosing of the probe drugs on Day 1 and Day 22. Participants will not receive any further food until 4 hours postdose on serial PK sampling days (Day 1 and Day 22).
- No water is allowed from 1 hour prior to dosing until 1 hour after dosing with ZX008 and/or probe drugs except for the glass of room temperature water needed to administer the study treatments (not to exceed 240mL). Water is allowed ad libitum at all other times. If necessary, additional water may be administered to allow dosing of any other permitted

medications, but the additional volume of water must be kept to a minimum. The amount of additional water should be documented in the source documents.

- All participants will receive standard meals for breakfast, lunch, and dinner at all other times.
- Participants will abstain from consumption of any food products with a known DDI impact (eg, grapefruit, grapefruit juice, Seville oranges, or products containing them) for at least 1 week before Day 1 and through discharge from the site on Day 26.

### **5.3.2 Caffeine, alcohol, and tobacco**

- Consumption of more than 600mg of caffeine/day (1 cup of coffee contains approximately 100mg of caffeine, 1 cup of tea approximately 30mg, and 1 glass of cola approximately 20mg) is not allowed within 35 days before Day 1 and through day of discharge from the site.
- From 72 hours prior to the administration of study treatments on Day 1 through day of discharge from the site, participants will abstain from alcohol.
- Use of tobacco products including nicotine-containing products such as patches, gum, vapes or e-cigarettes will not be allowed from 30 days before Day 1 through day of discharge from the site.

### **5.3.3 Activity**

- Participants will abstain from strenuous exercise from 24 hours prior to the administration of study treatments on Day -1 through day of discharge from the site. Participants may participate in light recreational activities during the study (eg, watching television, reading).

## **5.4 Screen failures**

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

If a study participant does not meet the criteria for participation in this study (screen failure) at Screening or on Day -1 due to an out-of-range laboratory result or a minor illness, the participant can be rescreened once at the discretion of the investigator. Provided all enrollment criteria are met at the second screening, the study participant can be included.

Study participants may be included if the repeat values for the laboratory screening criteria are within normal ranges and/or if repeat values show normalization of the out-of-range safety laboratory values, and/or after the study participant makes a complete recovery from the mild illness, and if all other screening criteria are met.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.

For study participants otherwise fully eligible, but not able to enter the treatment period as planned for logistical reasons, rescreening may be allowed at the discretion of the investigator, following discussion with the UCB Study Physician or delegate.

Rescreened participants should be assigned a new participant number.

## 6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment or marketed product(s) intended to be administered to a study participant according to the study protocol.

Each participant will receive the following treatments:

- Treatment Period 1 – a single dose of the cocktail of probe drugs on Day 1
- Treatment Period 2 – repeat oral doses of ZX008 (15mg bid) from Day 6 through Day 25 (morning dose only), and a single dose of the cocktail of probe drugs on Day 22

### 6.1 Treatments administered

An overview of study treatments to be administered during the study is provided in [Table 6.1](#).

**Table 6.1: Study treatments**

|                                | Treatment Periods 1 and 2                                                                                             | Treatment Period 2                                                                                                                                                                         |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Intervention name</b>       | Midazolam, metformin, bupropion                                                                                       | ZX008 (fenfluramine HCl)                                                                                                                                                                   |
| <b>Type</b>                    | Drug                                                                                                                  | Drug                                                                                                                                                                                       |
| <b>Dose formulation</b>        | Syrup (midazolam HCl, 2mg/mL)<br>Tablet (metformin IR)<br>Tablet (bupropion)                                          | Solution (clear) containing 2.5mg/mL fenfluramine HCl                                                                                                                                      |
| <b>Unit dose strengths</b>     | 2mg (midazolam HCl)<br>500mg (metformin HCl)<br>75mg (bupropion HCl)                                                  | 15mg                                                                                                                                                                                       |
| <b>Dosage levels</b>           | Single dose of each<br>2mg (midazolam HCl)<br>500mg (metformin HCl)<br>75mg (bupropion HCl)                           | 15mg bid (30mg/day)                                                                                                                                                                        |
| <b>Route of administration</b> | Oral                                                                                                                  | Oral                                                                                                                                                                                       |
| <b>Dosing instructions</b>     | Administer with no more than 240mL room temperature water.<br>For details, refer to the USPI and IMP Handling Manual. | May be administered with room temperature water, where the total volume of ZX008 oral solution and water does not exceed 240mL.<br>For details, refer to the USPI and IMP Handling Manual. |
| <b>Use</b>                     | Experimental                                                                                                          | Experimental                                                                                                                                                                               |

**Table 6.1: Study treatments**

|                                            | Treatment Periods 1 and 2                                                                                                                                                                                                                                                                                                                   | Treatment Period 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>NIMP and IMP</b>                        | NIMP                                                                                                                                                                                                                                                                                                                                        | IMP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Sourcing</b>                            | Commercial products will be used for the study sourced locally at the site.                                                                                                                                                                                                                                                                 | Provided centrally by the Sponsor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Packaging and labeling</b>              | Supplied by the site's pharmacy<br>The NIMP is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each NIMP carton will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the IMP Handling Manual. | Supplied as 2.5mg/mL fenfluramine HCl in an aqueous oral solution that contains 2.2mg/mL of fenfluramine free base and inactive excipients in white, plastic bottles with a child resistant closure. Before dispensing, the site pharmacist will insert a press-in bottle adapter into the dispensing bottle. Site pharmacy will provide 3mL or 6mL calibrated oral dosing syringes.<br>The IMP is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each IMP carton will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the IMP Handling Manual. |
| <b>Excipients</b>                          | As per USPI of the drug products sourced by the site                                                                                                                                                                                                                                                                                        | Cherry flavor, citric acid, ethylparaben, hydroxyethylcellulose, methylparaben, potassium citrate, sucralose, and water                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Current/Former name(s) or alias(es)</b> | None                                                                                                                                                                                                                                                                                                                                        | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

GMP=Good Manufacturing Practice; HCl=hydrochloride; IMP=investigational medicinal product; IR=immediate release; NIMP=non-investigational medicinal product; USPI=United States Prescribing Information

## 6.2 Preparation, handling, storage, and accountability requirements

UCB will provide the investigator or the site with adequate quantities of ZX008. Commercially available forms of midazolam, bupropion, and metformin (as indicated in [Table 6.1](#)) will be supplied by the site. The site pharmacy will prepare the study treatments for each participant.

Further details on the preparation of the study treatments will be provided in the IMP Handling Manual.

Appropriate storage temperature and transportation conditions will be maintained for the study treatments from the point of manufacture up to delivery of the study treatments. Study treatments must be stored at 15°C to 25°C (59°F to 77°F); do not refrigerate or freeze. The process for managing temperature excursions is defined in the IMP Handling Manual; see the IMP Handling Manual for additional detail. Directions for handling of unused study treatments are provided in the IMP Handling Manual.

The investigator (or designee) must confirm that appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment. Drug supplies must be stored in a secure, limited access storage area in the recommended storage conditions.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

Further guidance and information for the final disposition of unused study treatment are provided in the IMP Handling Manual.

### **6.2.1 Drug accountability**

Dispensing of study treatment will be documented in ClinBase to record study treatment dispensing on a by participant basis and will serve as source documentation during the course of the study. Details of any study treatment lost, damaged (due to breakage or wastage), not used, partially used, or disposed of at the study site must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study treatment until returned or destroyed.

The investigator may assign some of the investigator's duties for study treatment accountability at the study site to an appropriate pharmacist/designee.

The investigator must ensure that the study treatment is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers/partially used), unused, damaged, and/or expired study treatment must be reconciled and destroyed at the site according to local laws, regulations, and UCB standard operating procedures (SOPs). Study treatment intended for the study cannot be used for any other purpose than that described in this protocol.

### **6.3 Measures to minimize bias: randomization and blinding**

Not applicable in this one-arm open-label study. All participants will receive the same treatments in the same sequence. Participant numbers will be assigned at the site in an unblinded fashion and will be entered into ClinBase.

### **6.4 Treatment compliance**

For all participants, the study treatments (the cocktail of probe drugs and ZX008) will be administered at the site under direct supervision of the investigator or designated clinical personnel.

The date and exact time of each dose administered will be recorded in the source documents. The dose of study treatments and study participant identification (ID) will be confirmed at the time of dosing by ClinBase auto-check. Study site personnel will examine each participant's mouth to ensure that the entire dose of the study treatments was ingested.

If a participant is not administered the study treatments, the reason for the missed dose will be recorded.

Drug accountability must be recorded on the Drug Accountability form.

If a participant is found to be persistently noncompliant, the Sponsor, in conjunction with the investigator, will make a decision as to whether the participant should be withdrawn from the study.

### **6.5 Concomitant medication(s)/treatment(s)**

#### **6.5.1 Permitted concomitant treatments (medications and therapies)**

The following concomitant medications are permitted during the study:

Acetaminophen (paracetamol) for the treatment of mild symptoms (eg, headache) is permitted during the study (up to 2g per day).

Study participants are allowed vaccinations up to 14 days prior to the initiation of study treatment administration. Vaccine administration will be recorded as a prior medication in the eCRF.

Use of hormonal contraception is permitted (examples of acceptable forms include estrogen- and progesterone-containing contraceptives, and progesterone-only contraceptives).

No other concomitant medications are allowed during this study unless deemed necessary for the welfare of the participant during the study at the discretion of the investigator.

#### **6.5.2 Prohibited concomitant treatments (medications and therapies)**

The following concomitant medications are prohibited during the study:

Any hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin) within 30 days before the first administration of cocktail of probe drugs and during the study.

All prescription drugs, including vaccinations, over-the-counter medications, herbal/traditional medicines and dietary supplements (excluding medicines for external/topical use) are prohibited

within 14 days before first administration of study treatments on Day 1 and during the study until the Safety Follow-Up Visit, unless required to treat an AE.

If a participant requires or takes any prohibited medication, the investigator will (where possible) discuss with the UCB Study Physician and a decision will be made whether the participant may continue in the study or must be withdrawn.

### **6.5.3 Rescue medication**

Rescue medications are not applicable to this Phase 1 study in healthy participants.

### **6.6 Dose modification**

Not applicable. No dose modification is allowed in this study.

### **6.7 Criteria for study hold or dosing stoppage**

UCB will hold further dosing if the following criteria are met during the course of the study, and following case review to confirm causality and seriousness and/or severity of reported events:

- One participant has an SAE considered related to ZX008 or any of the probe drugs (including those considered probable/likely or possibly related to ZX008 or any of the probe drugs)
- Liver chemistry stopping criteria specified in Section 7.1.1
- QTc stopping criteria specified in Section 7.1.2

### **6.8 Treatment after the end of the study**

There are no plans for participant continued care after the end of the study, because participants are healthy.

## **7 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL**

### **7.1 Discontinuation of study treatment**

The study treatments will be stopped if the study participant develops a medical condition (or laboratory abnormality, or ECG change) that, in the opinion of the investigator, compromises the study participant's ability to participate or compromises the study participant's safety. The study treatments will be stopped if the study participant withdraws consent, as detailed in Section 7.2.

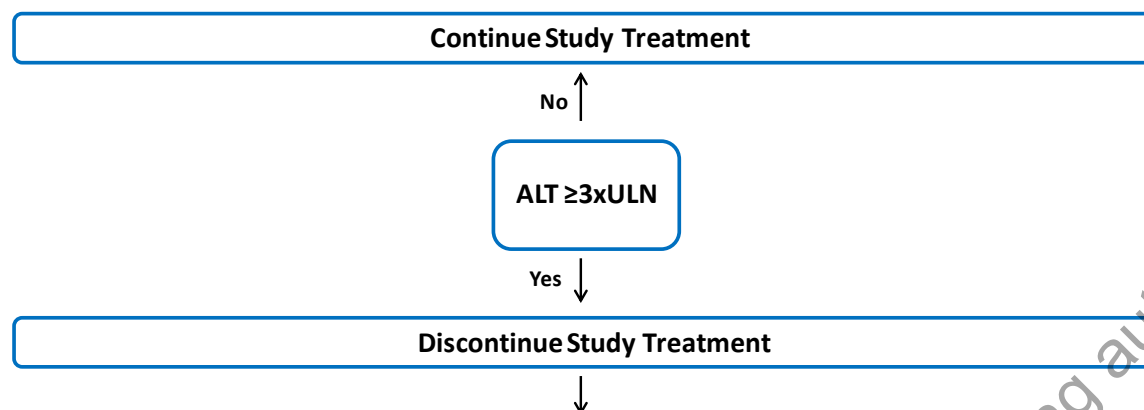
If a study participant has a hypersensitivity reaction (regardless of its severity) that, in the opinion of the investigator, could be associated with the study treatments, the study participant will be discontinued from further dosing immediately. The study participant should be rapidly and thoroughly assessed as described in Section 8.3.6.

In all cases, the study participant should be followed until the condition has resolved as agreed by the investigator and the UCB Study Physician. If a study participant discontinues study treatments, no restart will be allowed.

#### **7.1.1 Liver chemistry stopping criteria**

Study treatment will be discontinued immediately and permanently for a participant if liver chemistry stopping criteria as outlined in Figure 7.1 are met or if the investigator believes that it is in best interest of the participant.

**Figure 7.1: Phase 1 liver chemistry stopping algorithm**



ALT=alanine aminotransferase; ULN=upper limit of normal

Specific assessments and follow-up actions for potential drug-induced liver injury (PDILI) are provided in Appendix 6.

### 7.1.2 QTc stopping criteria

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from the study.

- QTcF >500msec
- Change from Baseline: QTcF >60msec

If a clinically significant finding is identified (including, but not limited to, changes from Baseline in QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the Schedule of Activities ([Table 4.1](#)) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed. Refer to Section [8.2.4](#) for more details on ECG recordings.

## 7.2 Participant discontinuation/withdrawal from the study

Participants are free to withdraw from the study at any time, without prejudice to their continued care.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the Schedule of Activities (Table 1.1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant develops an illness that would interfere with his/her continued participation.
2. Participant is noncompliant with the study procedures or medications in the opinion of the investigator.
3. Participant takes prohibited concomitant medications as defined in this protocol.
4. Participant withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The Sponsor or a regulatory agency requests withdrawal of the participant.
7. Participant has active suicidal ideation as indicated by a positive response (Yes) to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The study participant should be referred immediately to a mental healthcare professional and must be withdrawn from the study.

For the 18 evaluable participants planned, a total of 22 participants are planned to be enrolled. As it is not expected that >4 participants will be withdrawn from the participation in this study, replacement of withdrawn participants is not planned. Withdrawn participants may be replaced if otherwise the expected number of evaluable participants will be <18.

Investigators should contact the UCB Study Physician or the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance.

### 7.3 Lost to follow up

A participant will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant) and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow up documented in the eCRF.

## 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities ([Table 1.1](#)).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 400mL over a 30-day period or 550mL over an 8-week period (maximum of 10.5mL/kg).

### 8.1 Efficacy assessments

Not applicable to this study in healthy participants.

### 8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities ([Table 1.1](#)).

#### 8.2.1 Demographic

Participant demographics (sex, race, ethnicity, age, height, and weight) will be recorded at the Screening Visit.

#### 8.2.2 Physical examination

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal, and hepatic systems.

A brief physical examination will include, at a minimum, assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen).

In the event of significant AEs occurring, a symptom-driven physical examination may be performed at the discretion of the investigator.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

### **8.2.3 Vital signs**

Vital signs will be measured in a semisupine position after 5 minutes rest and will include temperature, SBP and DBP, and pulse and respiratory rate. Three readings of blood pressure and pulse will be taken at least 1 minute apart. The first reading should be rejected. The second and third readings should be averaged, the average value should be recorded in the eCRF.

### **8.2.4 Electrocardiograms**

Single 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

All ECG recordings should be taken with the study participant resting in the semisupine position for at least 5 minutes before the recording and at least 10 minutes prior to dosing (predose recordings).

In the case of clinically significant ECG findings (including QTcF >500msec, change from Baseline: QTcF >60msec, see Section 7.1.2), 2 additional ECGs will be performed. The 3 individual ECG tracings should be obtained as closely as possible in succession. All 3 individual ECG tracings are to be recorded. Any new clinically relevant finding should be reported as an AE.

All ECGs will be performed at the site and read locally by the investigator.

### **8.2.5 Echocardiograms**

Echocardiograms will be conducted at Screening, at discharge from the site (Day 26), and at the Safety Follow-Up Visit 90 days after discharge from the site, or after early termination or withdrawal.

Specifically, the occurrence of clinically significant abnormal valve regurgitation and/or increased pulmonary arterial pressure will be reported.

All ECHOs will be conducted on standard equipment and digitally transferred for central reading to the ECHO core laboratory. Overall interpretation for ECHO results will be normal, abnormal not clinically significant, and abnormal clinically significant.

### **8.2.6 Clinical safety laboratory assessments**

See Appendix 2 for the list of clinical laboratory tests to be performed.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the investigator or Medical Monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the Schedule of Activities (Table 1.1).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the eCRF.

### **8.2.7 Suicidal risk monitoring**

ZX008 is considered to be central nervous system-active. In addition, there have been some reports of suicidal ideation or behavior as reported in the product label when it has been given to some participants with Dravet syndrome and Lennox-Gastaut syndrome. The Sponsor considers it important to monitor for such events before and during this clinical study.

ZX008 is considered to be an anti-epileptic study treatment. There has been some concern that anti-epileptics may be associated with an increased risk of suicidal ideation or behavior when given to some participants with epilepsy. Although this study treatment or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to healthy participants, the Sponsor considers it important to monitor for such events before or during this clinical study.

Participants being treated with ZX008 will be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing ZX008 in participants who experience signs of suicidal ideation or behavior. Participants treated with ZX008 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior.

Consideration should be given to discontinuing ZX008 in participants who experience signs of suicidal ideation or behavior. Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used at Screening as well as to assess suicidal ideation and behavior that may occur during the study (see Schedule of Activities, [Table 1.1](#)). Refer to Section 7 for suicidality withdrawal criteria.

## **8.3 Adverse events and serious adverse events**

AEs will be reported by the participant.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study (see Section 7).

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent adverse events (TEAEs) and treatment-emergent SAEs will be published.

### **8.3.1 Time period and frequency for collecting AE and SAE information**

All AEs and SAEs will be collected from the signing of the ICF until the Safety Follow-Up Visit at the time points specified in the Schedule of Activities ([Table 1.1](#)).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no study treatment was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the study treatment), up to the Safety Follow-Up Visit for each participant, and to also inform participants of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the study treatment must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

### **8.3.2 Method of detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### **8.3.3 Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious adverse events of special interest (AESIs, as defined in Section 8.3.6), will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

### **8.3.4 Regulatory reporting requirements for SAEs**

Prompt notification of an SAE by the investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary. The reporting of SUSARs will be in adherence to requirements of EU pharmacovigilance legislation, CT legislation and guidance, Clinical Trial Regulation EU 536/2014; CT-3 and all other applicable local regulations.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

### 8.3.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until the end of the pregnancy. Pregnancy information will be collected from the signing of the ICF until the Safety Follow-Up Visit.

If a pregnancy is reported, the investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

The participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The participant should return for an early discontinuation visit.
- The participant should immediately stop the intake of the study treatment as instructed at the early discontinuation visit.
- A Safety Follow-Up Visit should be scheduled at 12 months after the delivery date (Section 10.4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 8.3.6 Adverse Event of Special Interest

An adverse event of special interest (AESI) is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. For ZX008, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, defined as  $\geq 3 \times \text{ULN}$  ALT or AST with coexisting  $\geq 2 \times \text{ULN}$  total bilirubin in the absence of  $\geq 2 \times \text{ULN}$  ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Valvular heart disease
  - any valvular abnormality reported on the ECHO.
- Pulmonary arterial hypertension
  - any ECHO finding suggestive of increased pulmonary arterial pressure, including pulmonary arterial SBP above 35mmHg.

## 8.4 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the study treatment so that investigators, clinical study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The UCB Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient

Safety representative. In addition to the SAEs, laboratory abnormalities will also be monitored for safety signal detection.

As appropriate for the stage of development and accumulated experience with the study treatment, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

## 8.5 Treatment of overdose

For all participants, the study treatments (the cocktail of probe drugs and ZX008) will be administered at the site under direct supervision of the investigator or designated clinical personnel. Therefore, overdose is unlikely to occur.

In case of overdose with any of the probe drugs (midazolam, bupropion, metformin), the respective product labels should be consulted for instructions.

For this study, any dose of ZX008 greater than 4 times the planned dose within a 24-hour time period [ $\pm 2$  hours] will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms, or if the act of taking the excess study treatment itself is an AE or SAE (eg, suicide attempt).

There is no available specific antidote to the overdose reactions of ZX008. In the event of overdose, standard medical practice for the management of drug overdosage should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with ZX008.

In the event of an overdose, the investigator/designee should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until fenfluramine can no longer be detected systemically (at least 9 days).
3. Obtain a plasma sample for PK analysis preferably within 4 hours after the overdose until 2 days after the final dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

## 8.6 Pharmacokinetics

Blood samples of approximately 6mL per time point will be collected for measurement of plasma concentrations of all 3 probe drugs and their metabolites, as well as 4mL per time point for the measurement of fenfluramine and norfenfluramine as specified in the Schedule of Activities ([Table 1.1](#)). Urine samples will be collected for measurement of urine concentrations of metformin.

Additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Sponsor. Instructions for the collection, handling, and processing of biological samples (for plasma and urine PK) will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample must be recorded. The plasma concentrations of all probe drugs and their metabolites will be measured using sensitive and validated bioanalytical methods. Urine concentrations of metformin will be determined by a sensitive and validated method. Bioanalysis of fenfluramine and norfenfluramine in plasma samples will be conducted by a validated liquid chromatography coupled with tandem mass spectrometry assay.

Collection windows for the scheduled PK blood samples (predose and after dose administration) and the maximum deviations from scheduled sampling times considered irrelevant for PK are defined in [Table 8.1](#).

**Table 8.1: Time windows for PK blood samples**

| PK blood sampling times | Deviation from scheduled time considered irrelevant |
|-------------------------|-----------------------------------------------------|
| 0 hours (predose)       | Within 60 minutes before dosing                     |
| 0.25 to 1 hour          | ±2 minutes                                          |
| 1.5 to 12 hours         | ±10 minutes                                         |
| 24 to 48 hours          | ±30 minutes                                         |
| >48 hours               | ±60 minutes                                         |

PK=pharmacokinetic(s)

Samples will be used to evaluate the PK of all 3 probe drugs and their metabolites, as well as fenfluramine and norfenfluramine. Plasma and urine samples collected for PK analyses may also be used to evaluate safety aspects related to concerns arising during or after the study. Surplus PK samples may be stored and used for potential future biomarker research (including assay development/optimization), but not for future genetic biomarker research.

The following primary noncompartmental PK endpoints will be compared for the probe drugs after a single dose administered alone (Day 1) and following 17 days of ZX008 administration (Day 22):

- Maximum observed concentration [ $C_{max}$ ] - Time Frame: predose and at multiple time points (up to 96 hours) postdose
- Area under the curve from 0 to infinity [AUC] - Time Frame: predose and at multiple time points (up to 96 hours) postdose
- Area under the curve from 0 to the time of the last quantifiable concentration [AUC(0-t)] – Time Frame: predose and at multiple time points (up to 96 hours) postdose

with “predose” and “postdose” referring to administration of the probe drugs.

The following noncompartmental PK endpoints will be estimated for the probe drugs administered alone (Day 1) and following 17 days of ZX008 administration (Day 22):

- Time to  $C_{\max}$  [ $t_{\max}$ ], last observed (quantifiable) concentration [ $C_{\text{last}}$ ], time of  $C_{\text{last}}$  [ $t_{\text{last}}$ ], apparent total body clearance [ $CL/F$ ] calculated as  $CL/F = \text{Dose}/AUC$ , apparent volume of distribution [ $V_z/F$ ], calculated as  $V_z/F = (CL/F)/\lambda_z$ , first order terminal elimination rate constant [ $\lambda_z$ ], and half-life [ $t_{1/2}$ ] – Time Frame: predose and at multiple time points (up to 96 hours) postdose
- Cumulative amount of unchanged drug excreted in urine [ $A_e$ ] of metformin and the fraction of the dose excreted unchanged in urine [ $f_e$ ] of metformin calculated as  $A_e/\text{Dose} \times 100$  – Time Frame: predose and at multiple time points (up to 96 hours) postdose
- Renal clearance [ $CL_R$ ] of metformin calculated by dividing  $A_e$  by  $AUC$  – Time Frame: predose and at multiple time points (up to 72 hours) postdose

The following noncompartmental PK endpoints will be estimated for the metabolites (1-hydroxymidazolam and hydroxybupropion [or [S,S]-hydroxybupropion if an enantioselective assay is selected]) when the probe drugs are administered alone (Day 1) and following 17 days of ZX008 administration (Day 22):

- $C_{\max}$ ,  $AUC(0-t)$ ,  $AUC$ ,  $t_{\max}$ ,  $C_{\text{last}}$ ,  $t_{\text{last}}$ ,  $\lambda_z$ , and  $t_{1/2}$  – Time Frame: predose and at multiple time points (up to 96 hours) postdose
- Metabolite to parent ratio for  $C_{\max}$ ,  $AUC(0-t)$ , and  $AUC$  – Time Frame: predose and at multiple time points (up to 96 hours) postdose

Trough (predose) plasma concentrations of fenfluramine and norfenfluramine will be analyzed from Day 19 to Day 23.

## 8.7 Genetics

Samples for the genetic testing will be collected at screening to determine potential variations in the genes for 2 metabolic enzymes (CYP2B6 and CYP3A4) that are integral to the study objectives. Genotype and the associated phenotype for the two CYP2B6 and CYP3A4 of interest will be documented. Participants must agree to this genetic testing to be eligible for enrollment in the study. Details regarding sample collection, processing, and shipping will be provided in the laboratory manual. See also Appendix 5 (Section 10.5).

## 8.8 Biomarkers

Biomarkers are not evaluated in this study.

## 8.9 Medical resource utilization and health economics

Medical resource utilization and health economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP). The term “treatment” refers to the treatment under consideration, being probe drugs alone (Days 1 to 5), ZX008 15mg bid alone (Days 6 to 21), or probe drugs concomitant with ZX008 15mg bid (Days 22 to 26).

## 9.1 Definition of analysis sets

Analysis sets are defined in Table 9.1.

**Table 9.1: Analysis sets**

| Analysis sets                     | Definition/criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>All study participants set</b> | All participants who have signed the ICF.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Safety set</b>                 | All study participants who receive at least 1 dose of the study treatments will be included.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>PKS</b>                        | <p>All study participants who receive at least 1 dose of the study treatments and have at least 1 quantifiable postdose PK concentration measurement.</p> <p>If a study participant in the PKS is missing individual time points or they are otherwise unobservable, they will be included in the PKS, but those time points will be omitted from the PK summaries, as appropriate.</p> <p>Data from participants who experience emesis during the course of the study might be excluded from the statistical analysis, depending on the time relative to the PK sampling and the frequency of the event, but the plasma concentration data will be flagged and listed.</p> <p>Study participants in the PKS may not have a complete set of PK endpoints as some parameters may not be able to be calculated based on the PK concentrations collected.</p> |

ICF=informed consent form; PK=pharmacokinetic(s); PKS=pharmacokinetic set

## 9.2 General statistical considerations

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using SAS® (SAS Institute, Cary, NC, US) Version 9.4 or higher using validated program code according to relevant SOP.

For continuous variables, summary statistics will include number of study participants, mean, median, standard deviation (SD), minimum, and maximum. Categorical endpoints will be summarized using number of study participants, frequency, and percentages.

Tables, listings, and graphical displays will be provided by treatment and/or time point.

Unless otherwise stated, the Baseline for the safety assessments will be the last assessment prior to the administration of the cocktail of probe drugs on Day 1. Measurement of specific Baseline values will be described in the SAP.

## 9.3 Planned outcome analyses

### 9.3.1 PK endpoint analyses

Pharmacokinetics will be determined by noncompartmental analysis in Phoenix WinNonlin®. Plasma PK endpoints will be computed using actual blood sampling time points.

All PK endpoints will be listed and summarized using the pharmacokinetic set (PKS).

Pharmacokinetics endpoints will be calculated for each participant for each probe drug and their metabolites. Individual plasma concentrations of the 3 probe drugs and their metabolites over time in plasma, as well as urine concentrations of metformin over time, and the primary PK endpoints will be summarized by treatment (probe drugs alone, probe drugs with ZX008 15mg bid) using descriptive statistics (number of observations, geometric mean, lower and upper 95% confidence interval [CI] of the geometric mean, geometric coefficient of variation [CV], arithmetic mean, SD, median, minimum, and maximum). Individual plasma concentrations of fenfluramine and norfenfluramine on Days 19, 20, 21, 22, and 23 (Treatment Period 2) will be summarized similarly. Descriptive statistics of plasma concentrations will be calculated if at least two-thirds of the individual data points are quantifiable ( $\geq$  lower limit of quantification).

Individual plasma concentration-time profiles will be displayed graphically on a linear scale and semilogarithmic scale. Plasma concentrations of the probe drugs and their metabolites will be displayed superimposed in 1 plot for all corresponding treatments (ie, probe drugs alone in Treatment Period 1, probe drugs with ZX008 15mg bid in Treatment Period 2). Geometric mean profiles (with and without corresponding lower and upper limit of the 95% CI) will be displayed in the same way.

Urine PK endpoints of metformin only will be computed from the individual urine concentrations and volume of urine excreted using a noncompartmental approach.

Urine collections noted as “No Void” will be treated as zero in volume, and cumulative and derived endpoints will be included in the summary statistics. Cumulative urine PK endpoints (eg,  $A_e$ ) and derived endpoints (eg,  $f_e$ ) after a missing sample (eg, void missing/lost, volume not recorded) will be presented with a flag alongside, but excluded from summary statistics.

#### **9.3.1.1 Primary endpoint analyses: potential effect of ZX008 on the single-dose PK of probe drugs**

All PKS participants who have a sufficient number of bioanalytical measurements to calculate reliable estimates for the primary noncompartmental PK endpoints for either treatment (probe drugs administered alone and with ZX008 at steady state) will be included in the statistical analysis. If a participant does not have primary noncompartmental PK endpoints calculated for both treatments of a specific probe drug, they will be excluded from the main statistical analysis for that specific probe drug but will be included in a sensitivity analysis. Potential DDI effects will be evaluated by mixed effects analysis of variance (ANOVA) for logarithmically transformed (base e) primary PK endpoints of each probe drug, including treatment (administered alone and with ZX008 at steady state) as a fixed effect and study participant as a random effect.

The least-squares mean difference between treatments (Treatment Period 2 versus Treatment Period 1) will be calculated along with 90% CI for the primary PK endpoints of midazolam, bupropion and metformin. The data will be back-transformed to provide a point estimate of the geometric mean ratio (GMR) and its 90% CI for the primary PK endpoints of midazolam, bupropion and metformin. The reference treatment will be the probe drug administered in the absence of ZX008.

If the 90% CIs of GMR of all key PK parameters, ie, AUC, AUC(0-t), and  $C_{max}$  of each probe drug fall within the range of 0.80 to 1.25, the study can be interpreted as negative for DDI effects.

### 9.3.2 Other efficacy/other outcome analyses

The following noncompartmental PK endpoints, apart from  $t_{\max}$  and  $t_{\text{last}}$ , will be listed and summarized by treatment using descriptive statistics as for the PK endpoints described in Section 9.3.1:

- $t_{\max}$ ,  $C_{\text{last}}$ ,  $t_{\text{last}}$ ,  $CL/F$ ,  $V_z/F$ ,  $\lambda_z$ , and  $t_{1/2}$  of the probe drugs when administered alone and following 17 days of ZX008 administration, ie, in Treatment Period 1 and Treatment Period 2, respectively - Time Frame: predose and at multiple time points (up to 96 hours) postdose on Day 1 and Day 22
- $C_{\max}$ ,  $AUC(0-t)$ ,  $AUC$ ,  $t_{\max}$ ,  $C_{\text{last}}$ ,  $t_{\text{last}}$ ,  $\lambda_z$ , and  $t_{1/2}$  of 1-hydroxymidazolam and hydroxybupropion (or [S,S]-hydroxybupropion, if an enantioselective assay is selected) when probe drugs are administered alone and following 17 days of ZX008 administration - Time Frame: predose and at multiple time points (up to 96 hours) postdose on Day 1 and Day 22
- Metabolite to parent ratio for  $C_{\max}$ ,  $AUC(0-t)$ , and  $AUC$  of 1-hydroxymidazolam and midazolam, and hydroxybupropion and bupropion (or [S,S]-hydroxybupropion and S-bupropion, if an enantioselective assay is selected), when probe drugs are administered alone and following 17 days of ZX008 administration - Time Frame: predose and at multiple time points (up to 96 hours) postdose on Day 1 and Day 22
- $A_e$  (cumulative amount of unchanged drug excreted in urine) and  $f_e$  (fraction of dose excreted unchanged in urine) for metformin when administered alone and following 17 days of ZX008 administration - Time Frame: predose and at multiple time points (up to 72 hours) postdose on Day 1 and Day 22
- Metformin  $CL_R$ , when administered alone and following 17 days of ZX008 administration - Time Frame: predose and at multiple time points (up to 72 hours) postdose on Day 1 and Day 22

with “predose” and “postdose” referring to administration of the probe drugs.

For  $t_{\max}$  of each probe drug, a nonparametric analysis will be performed to assess the difference between treatments. The PK parameters  $t_{\max}$  and  $t_{\text{last}}$  will be summarized using number of observations, median, minimum, and maximum for each treatment.

Additionally, trough (predose) plasma concentrations of fenfluramine and norfenfluramine on Days 19, 20, 21, 22, and 23 in Treatment Period 2 will be summarized.

## 9.4 Planned safety and other analyses

### 9.4.1 Safety analyses

All safety analyses will be performed using the Safety Set.

#### 9.4.1.1 Extent of exposure

Administration of treatments will be listed for all study participants in the Safety Set. The listing will include study participant ID, visit, and the date and time of administration of each dose.

#### 9.4.1.2 AEs

All AEs will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) and characterized as pretreatment (prior to the first dose) and treatment-emergent

according to the administration of study treatments. Treatment-emergent adverse events (TEAEs) will be assigned to the administration of the cocktail of probe drugs alone, ZX008 alone, or the combined administration depending on the start date and time of the TEAE. The TEAE will be attributed to the most recent treatment received.

All AEs captured in the database will be listed in by-participant data listings including reported term, preferred term, treatment, intensity, relationship to study treatments, and action taken; however, only TEAEs will be summarized.

The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class and preferred term by treatment. The occurrence and incidence of TEAEs will also be summarized by intensity and by relationship to treatment. Any AEs leading to discontinuation, AESIs, and SAEs will also be listed.

#### **9.4.1.3 Additional safety assessments**

##### **9.4.1.3.1 Physical examination**

Physical examination abnormalities will be listed, including clinical significance.

##### **9.4.1.3.2 Vital signs**

Vital signs and changes from Baseline will be summarized by descriptive statistics for each time point and treatment.

##### **9.4.1.3.3 Electrocardiograms**

Descriptive statistics will be presented for each ECG parameter by assessment time point and treatment. Changes from Baseline will be summarized in a similar manner.

Abnormal findings for the ECG will be listed.

##### **9.4.1.3.4 Echocardiograms**

Frequency count for overall interpretation will be presented by treatment and time point of collection. Echocardiogram results will be listed by participant and time point of collection.

##### **9.4.1.3.5 Clinical laboratory evaluations**

Laboratory test results (serum chemistry, hematology, and urinalysis) and changes from Baseline will be summarized by descriptive statistics at each time point by treatment. Values outside the reference range will be flagged in the listings.

##### **9.4.1.3.6 Assessment of suicidality**

The C-SSRS questionnaire responses will be listed.

#### **9.4.2 Other analyses**

The phenotypes of CYPs in each participant will be categorized as determined by the testing laboratory. Genotypes and associated phenotypes in individual participants will be listed and summarized.

Baseline demographic and background variables will be summarized for all study participants. The number of participants who enter Treatment Period 1 and the number and percentage of participants who complete the study will be presented. Frequency and percentage of participants

who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

## 9.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the PK and key safety for an individual study participant. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Protocol deviations will be reviewed as part of the ongoing data cleaning process and important deviations will be identified and documented. Further details on the impact of important protocol deviations on analysis sets will be provided in the SAP.

## 9.6 Handling of dropouts or missing data

There will be no special procedures for handling missing data. Handling of missing or partial dates and/or times for safety assessments will be described in the SAP.

## 9.7 Planned interim analysis and data monitoring

No interim analysis or data monitoring is planned.

## 9.8 Determination of sample size

A sufficient number of study participants will be screened to ensure that 22 study participants enter Treatment Period 1 (ie, are dosed with the cocktail of probe drugs), with the objective of having 18 study participants complete both treatment periods and have reliable primary PK endpoints for both treatment periods. It is not planned for dropouts to be replaced, but if more participants than expected withdraw from the study, study participants who are withdrawn may be replaced following a discussion between the investigator and Sponsor.

This study is not powered to formally test hypotheses for DDIs, but the number of participants included should be sufficient to provide reliable estimates of the magnitude and variability of the DDIs.

If it is expected that the GMR of AUC (or AUC(0-t) or  $C_{max}$ ) for midazolam in the presence versus absence of repeat doses of ZX008 at steady state is 1.00, a sample size of 18 will provide 95% certainty that a 90% CI for the GMR of AUC (or AUC(0-t) or  $C_{max}$ ) lies within the range of 0.80 to 1.25 (this range represents a precision of  $\pm 0.223$  about the difference of the means when data are logarithmically transformed [base e]). This also applies to the primary PK endpoints for bupropion and metformin. An intraparticipant coefficient of variation for AUC (or AUC(0-t) or  $C_{max}$ ) of 30% for each of the probe drugs was assumed.

Data obtained from the literature for a single dose of midazolam indicate an intraparticipant CV of 25% for clearance (CL) (Kharasch, 1999). As a sensitive CYP3A4 substrate, the variability estimate for midazolam used in the sample size assessment is expected to be representative of that for bupropion IR (Preskorn, 1989) and metformin IR (Smolders, 2017). Estimates of intraparticipant variability of CL and volume of distribution (V) of midazolam are commonly used to select the sample size for pertinent DDI studies. A more conservative estimate of 30% was used for all the probe drugs in this study, to allow for the uncertainty in the estimate of the variability.

Taking into account an estimated dropout rate of 20% of study participants, the inclusion of 22 study participants entering Treatment Period 1 is expected to be adequate to meet the objectives of the study.

The sample size chosen for this study is representative of similar DDI studies previously reported.

## **10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

### **10.1 Appendix 1: Regulatory, ethical, and study oversight considerations**

#### **10.1.1 Regulatory and ethical considerations**

The study will be conducted under the auspices of an IRB, as defined in local regulations, ICHGCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, ICF, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IRB for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB for the protocol.

The investigator will also promptly report to the IRB all changes in the study, all unanticipated problems involving risks to participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

The investigator will not make any changes in the study or study conduct without IRB approval, except where necessary to eliminate apparent immediate hazards to the participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB as allowed.

As part of the IRB requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB (based on IRB requirements), at intervals appropriate to the degree of participant risk involved, but no less than once per year. The investigator should provide a final report to the IRB following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements.

The appropriate IRB will also be informed by the investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the Sponsor (or its representative) with evidence of such IRB notification.

#### **10.1.2 Financial disclosure**

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the investigator and/or contract research organization agreements, as applicable.

### **10.1.3 Informed consent process**

Participant's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the investigator (or designee). Each participant will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the participant and by the person who conducted the informed consent discussion (investigator or designee). The participant must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB review, and regulatory inspection.

If the ICF is amended during the study, the investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB and use of the amended form.

All studies conducted at centers in the US must include the use of a Health Insurance Portability and Accountability Act authorization form.

The participant may withdraw his/her consent to participate in the study at any time.

A participant is considered enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

### **10.1.4 Data protection**

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant number assigned at Screening.

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

### **10.1.5 Dissemination of clinical study data**

This study will be registered, and results posted on public registries as required and in line with UCB policies. A plain language summary of results may also be written. Investigators may request access to anonymized study participant-level data and redacted study documents after product approval in the US and Europe. However, once the study completes, if the risk of re-identifying study participants is determined to be too high, then study participant-level data will not be made available.

### **10.1.6 Data quality assurance**

All participant data relating to the study will be recorded on an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the investigator for the minimum retention period mandatory under the applicable local laws and regulations. The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

#### **10.1.6.1 Case report form completion**

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

### **10.1.7 Source documents**

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original data, documents, and records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG, or other printouts, completed scales, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

The eCRF may be considered source data if the eCRF is the location of the original recording (ie, there is no other written or electronic record of data). The following data will be recorded directly in the eCRF and will not appear in a separate source document as defined above.

Source documents that are computer-generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the participant's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records, ECGs, and ECHOs, must be saved and stored as instructed by UCB (or designee).

### **10.1.8 Study and site start and closure**

#### **The start of recruitment**

The start of recruitment is the first participant's first visit and is also the start date of the clinical study.

#### **Study/site termination**

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

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### **10.1.9 Publication policy**

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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## 10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

### Protocol-Required Safety Laboratory Assessments

| Laboratory Assessments          | Parameters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |           |                                                                                          |                                                                                                                         |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Hematology                      | Platelet count                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |           | <u>Red blood cell indices:</u><br>Mean corpuscular hemoglobin<br>Mean corpuscular volume | <u>White blood cell count with differential:</u><br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
|                                 | Red blood cell count                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |           |                                                                                          |                                                                                                                         |
|                                 | Hemoglobin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |           |                                                                                          |                                                                                                                         |
|                                 | Hematocrit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |           |                                                                                          |                                                                                                                         |
| Clinical Chemistry <sup>a</sup> | Blood Urea Nitrogen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Potassium | Aspartate Aminotransferase/ Serum Glutamic-Oxaloacetic Transaminase                      | Total and direct bilirubin                                                                                              |
|                                 | Creatinine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Sodium    | Alanine Aminotransferase/Serum Glutamic-Pyruvic Transaminase                             | Total Protein                                                                                                           |
|                                 | Glucose (fasted)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Calcium   | Alkaline phosphatase                                                                     |                                                                                                                         |
|                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |           | Gamma GT                                                                                 |                                                                                                                         |
| Routine Urinalysis              | <ul style="list-style-type: none"><li>• Specific gravity</li><li>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick</li><li>• Microscopic examination (if blood or protein is abnormal)</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                        |           |                                                                                          |                                                                                                                         |
| Other Screening Tests           | <ul style="list-style-type: none"><li>• Follicle-stimulating hormone and estradiol (at discretion of investigator to determine if the participant is postmenopausal)</li><li>• Serum alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)</li><li>• Serum or urine human chorionic gonadotropin pregnancy test (as needed for WOCBP)<sup>b</sup></li><li>• Serology (HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody)</li></ul> <p>All study-required laboratory assessments will be performed by the local laboratory. The results of each test must be entered into the eCRF.</p> |           |                                                                                          |                                                                                                                         |

<sup>a</sup> Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT  $\geq 3$ x upper limit of normal (ULN) and bilirubin  $\geq 2$ xULN ( $>35\%$  direct bilirubin) or ALT  $\geq 3$ xULN and international normalized ratio (INR)  $>1.5$ , if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

| Laboratory Assessments | Parameters |
|------------------------|------------|
|------------------------|------------|

- b Local urine testing will be standard for the protocol unless serum testing is required by local regulation, IRB, or the Schedule of Activities ([Table 1.1](#)).

Investigators must document their review of each laboratory safety report.

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### 10.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow-up, and reporting

#### Definition of AE

| AE definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.</li> <li>NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.</li> </ul> |

| Events <u>meeting</u> the AE definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).</li> <li>Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.</li> <li>New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.</li> <li>Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li> <li>Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.</li> </ul> |

| Events <u>NOT</u> meeting the AE definition                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.</li> <li>Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).</li> <li>Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.</li> </ul> |

#### Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>A SAE is defined as any untoward medical occurrence that, at any dose:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>a. Results in death</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>b. Is life-threatening</b><br>The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>c. Requires inpatient hospitalization or prolongation of existing hospitalization</b><br>In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.                                                                                                                                                                         |
| <b>d. Results in persistent disability/incapacity</b> <ul style="list-style-type: none"> <li>The term disability means a substantial disruption of a person’s ability to conduct normal life functions.</li> <li>This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>e. Is a congenital anomaly/birth defect</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>f. Important medical events:</b> <ul style="list-style-type: none"> <li>Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.</li> <li>Examples of such events include, but are not limited to, potential Hy’s Law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse; as well as any AE considered medically important or clinically significant by the investigator.</li> </ul> |

## Recording and follow-up of AE and/or SAE

|                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>AE and SAE recording</b>                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.</li> <li>The investigator will then record all relevant AE/SAE information in the eCRF.</li> </ul> |

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

#### Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the investigator must be mild, moderate, or severe.

#### Assessment of causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to UCB. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

#### Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

#### Reporting of SAEs

##### SAE reporting to UCB via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to UCB.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in [SERIOUS ADVERSE EVENT REPORTING](#).

## 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

### Definitions

#### Women of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### Contraception guidance

#### Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to **one** of the following from Screening to at least 5 terminal half-lives (approximately 7 days) after the final dose of ZX008:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for at least 5 terminal half-lives (approximately 7 days) after the final dose of ZX008.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from Screening to at least 5 terminal half-lives (approximately 7 days) after the final dose of ZX008.

### Female participants

Female participants of childbearing potential are eligible to participate if they agree to use at least 2 highly effective methods of contraception, ie, hormonal contraceptives plus a physical/barrier method, consistently and correctly as described in the table below.

#### Highly effective contraceptive methods<sup>a</sup>

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Highly effective contraceptive methods that are user dependent<sup>b</sup></b></p> <p>Failure rate of &lt;1% per year when used consistently and correctly.</p>                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p>Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<sup>c</sup></p> <ul style="list-style-type: none"> <li>• Oral</li> <li>• Intravaginal</li> <li>• Transdermal</li> </ul>                                                                                                                                                                                                                                                                                                                                  |
| <p>Progestogen only hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> <li>• Oral</li> <li>• Injectable</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>Highly effective methods that are user independent<sup>c</sup></b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p>Implantable progestogen only hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> <li>• Intrauterine device</li> <li>• Intrauterine hormone-releasing system</li> <li>• Bilateral tubal occlusion</li> </ul>                                                                                                                                                                                                                                                                                                           |
| <p><b>Vasectomized partner</b></p> <p>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.</p>                                                                                                                                                                                                                                                             |
| <p><b>Sexual abstinence</b></p> <p>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</p>                                                                                                                                                                           |
| <p><b>NOTES:</b></p> <p>a) In case of newly started contraception pills/intrauterine devices, the investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as to when these newly started methods would become effective.</p> <p>b) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.</p> |

c) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 5 terminal half-lives (approximately 7 days) after the final dose of ZX008.

### **Pregnancy testing**

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test as noted in Schedule of Activities ([Table 1.1](#)).
- Additional pregnancy testing (urine pregnancy test) will be done on Day -1 and Day 26.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- A highly sensitive serum pregnancy test will be performed by the local laboratory.

### **Male participants with partners who become pregnant**

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

### **Female participants who become pregnant**

Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek

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this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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## 10.5 Appendix 5: Genetics

### Use and analysis of DNA

- Consent to genotyping is required for participation in the study.
- Genetic variation may impact a participant's response to study treatment, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to study treatments. They may also be used to develop tests/assays, including diagnostic tests related to the study treatment. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers across the entire genome (as appropriate), but only as they relate to the aims of further understanding the response to ZX008 and probe drugs in this study.
- The samples may be analyzed as part of this study alone or as part of a multi-study assessment of genetic factors involved in the response to ZX008, and to understand the disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained for at least the duration of the study (including the approval of the clinical study report) but no longer than 3 years or other period as per local requirements.

For screen failures, genetic samples will be destroyed post CYP2B6 and CYP3A4 analysis.

## 10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments

Participants with PDILI must be assessed to determine if study treatment must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study treatment discontinuation to complete the final evaluation.

Study participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study treatment discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study treatment.

A specific monitoring plan must be agreed between the UCB study physician and the investigator for study participants who have ALT >5xULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal laboratory values).

| Liver Chemistry Stopping Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ALT-absolute</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p>ALT <math>\geq 3</math>xULN</p> <p>If ALT <math>\geq 3</math>xULN AND bilirubin <math>\geq 2</math>xULN (<math>\geq 35\%</math> direct bilirubin) or INR &gt;1.5, report as an SAE.<sup>a,b</sup></p> <p>See additional actions and follow-up assessments below.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Required actions and follow-up assessments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Follow-up assessments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>• <b>Immediately</b> discontinue study intervention.</li> <li>• Report the event to the Sponsor <b>within 24 hours</b>.</li> <li>• Complete the liver event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE.<sup>b</sup></li> <li>• Perform liver function follow-up assessments.</li> <li>• Monitor the participant until liver function test abnormalities resolve, stabilize, or return to Baseline (see <b>MONITORING</b>).</li> <li>• Consider the need for a toxicology screening.</li> </ul> <p><b>MONITORING:</b></p> <p><b>If ALT <math>\geq 3</math>xULN AND bilirubin <math>\geq 2</math>xULN or INR &gt;1.5:</b></p> <ul style="list-style-type: none"> <li>• Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within <b>24 hours</b>.</li> </ul> | <ul style="list-style-type: none"> <li>• Viral hepatitis serology<sup>c</sup></li> <li>• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend</li> <li>• Obtain blood sample for PK analysis 2 to 6 hours after the most recent dose<sup>d</sup></li> <li>• Serum CPK and LDH</li> <li>• Fractionate bilirubin, if total bilirubin <math>\geq 2</math>xULN</li> <li>• Complete blood count with differential to assess eosinophilia</li> <li>• Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the AE eCRF</li> <li>• Record use of concomitant medications (including acetaminophen, herbal remedies,</li> </ul> |

| Liver Chemistry Stopping Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ALT-absolute</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p>ALT <math>\geq 3 \times \text{ULN}</math></p> <p>If ALT <math>\geq 3 \times \text{ULN}</math> AND bilirubin <math>\geq 2 \times \text{ULN}</math> (&gt;35% direct bilirubin) or INR &gt;1.5, report as an SAE.<sup>a,b</sup></p> <p>See additional actions and follow-up assessments below.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Required actions and follow-up assessments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Follow-up assessments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>Monitor participant twice weekly until liver function test abnormalities resolve, stabilize, or return to Baseline.</li> <li>A specialist or hepatology consultation is recommended.</li> </ul> <p><b>If ALT <math>\geq 3 \times \text{ULN}</math> AND bilirubin &lt;2xULN and INR <math>\leq 1.5</math>:</b></p> <ul style="list-style-type: none"> <li>Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within <b>24 to 72 hours</b>.</li> <li>Monitor participants weekly until liver function abnormalities resolve, stabilize, or return to Baseline.</li> </ul> | <p>and other over-the-counter medications) on the concomitant medications eCRF</p> <ul style="list-style-type: none"> <li>Record alcohol use on the liver event alcohol intake eCRF</li> </ul> <p><b>If ALT <math>\geq 3 \times \text{ULN}</math> AND bilirubin <math>\geq 2 \times \text{ULN}</math> or INR &gt;1.5:</b></p> <ul style="list-style-type: none"> <li>Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins</li> <li>Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009])</li> <li>Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs</li> </ul> |

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; eCRF=electronic case report form; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic(s); RNA=ribonucleic acid; SAE=serious adverse event; ULN=upper limit of normal

<sup>a</sup> Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT  $\geq 3 \times \text{ULN}$ . Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

<sup>b</sup> All events of ALT  $\geq 3 \times \text{ULN}$  and bilirubin  $\geq 2 \times \text{ULN}$  (>35% direct bilirubin) or ALT  $\geq 3 \times \text{ULN}$  and INR >1.5 may indicate severe liver injury (**possible “Hy’s Law”**) and **must be reported as an SAE**. The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

<sup>c</sup> Hepatitis A immunoglobulin M antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

<sup>d</sup> PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant’s best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the

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time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

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**10.7      Appendix 7: Medical device adverse events, adverse device effects, serious adverse events, and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting**

Not applicable.

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**10.8      Appendix 8: Rapid alert procedures**

Not applicable.

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## **10.9      Appendix 9: Country-specific requirements**

Not applicable.

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## 10.10 Appendix 10: Abbreviations and trademarks

|                   |                                                                                |
|-------------------|--------------------------------------------------------------------------------|
| AE                | adverse event                                                                  |
| Ae                | cumulative amount of unchanged drug excreted in urine                          |
| AESI              | adverse event of special interest                                              |
| ALP               | alkaline phosphatase                                                           |
| ALT               | alanine aminotransferase                                                       |
| ANOVA             | analysis of variance                                                           |
| AST               | aspartate aminotransferase                                                     |
| AUC               | area under the curve from 0 to infinity                                        |
| AUC(0-t)          | area under the curve from 0 to the time of the last quantifiable concentration |
| CAR               | constitutive androstane receptor                                               |
| CI                | confidence interval                                                            |
| CL                | clearance                                                                      |
| CL/F              | apparent total body clearance                                                  |
| C <sub>last</sub> | last observed (quantifiable) concentration                                     |
| CL <sub>R</sub>   | renal clearance                                                                |
| C <sub>max</sub>  | maximum concentration                                                          |
| C-SSRS            | Columbia-Suicide Severity Rating Scale                                         |
| CV                | coefficient of variation                                                       |
| CYP               | cytochrome P450                                                                |
| DBP               | diastolic blood pressure                                                       |
| DDI               | drug-drug interaction                                                          |
| ECG               | electrocardiogram                                                              |
| eCRF              | electronic case report form                                                    |
| EMA               | European Medicines Agency                                                      |
| fe                | fraction of the dose excreted unchanged in urine                               |
| GCP               | Good Clinical Practice                                                         |
| GMR               | geometric mean ratio                                                           |
| HIV(-1/2Ab)       | human immunodeficiency virus (1 or 2 antibody)                                 |
| HRT               | hormone replacement therapy                                                    |

|            |                                                  |
|------------|--------------------------------------------------|
| ICF        | informed consent form                            |
| ICH        | International Council for Harmonisation          |
| ID         | identification                                   |
| IEC        | Independent Ethics Committee                     |
| IMP        | investigational medicinal product                |
| IND        | investigational new drug                         |
| INR        | international normalized ratio                   |
| IR         | immediate release                                |
| IRB        | Institutional Review Board                       |
| MATE1      | multidrug and toxin extrusion protein 1          |
| MedDRA     | Medical Dictionary for Regulatory Activities     |
| NCT number | ClinicalTrials.gov identifier                    |
| PAH        | pulmonary arterial hypertension                  |
| PASP       | pulmonary artery systolic pressure               |
| PDILI      | potential drug-induced liver injury              |
| PK         | pharmacokinetic(s)                               |
| PKS        | pharmacokinetic set                              |
| PXR        | pregnane X receptor                              |
| QTc        | QT interval corrected                            |
| QTcF       | QT interval corrected using Fridericia's formula |
| SAE        | serious adverse event                            |
| SAP        | Statistical Analysis Plan                        |
| SBP        | systolic blood pressure                          |
| SD         | standard deviation                               |
| SOP        | standard operating procedure                     |
| SUSAR      | suspected unexpected serious adverse reaction    |
| $t_{1/2}$  | terminal elimination half-life                   |
| TEAE       | treatment-emergent adverse event                 |
| $t_{last}$ | time of $C_{last}$                               |
| $t_{max}$  | time of $C_{max}$                                |
| ULN        | upper limit of normal                            |
| USPI       | United States Prescribing Information            |

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|             |                                                |
|-------------|------------------------------------------------|
| $V_z/F$     | apparent volume of distribution                |
| WOCBP       | woman/women of childbearing potential          |
| ZX008       | fenfluramine hydrochloride                     |
| $\lambda_z$ | first order terminal elimination rate constant |

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**10.11      Appendix 11: Protocol amendment history**

Not applicable.

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## SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol, according to Clinical Trial Regulation EU 536/2014, and according to current Good Clinical Practice.

Sponsor signatories are collected via an electronic signature workflow in the electronic document management system and are according to the approvers identified in sop-af-009924, List of reviewers and approvers of clinical documents and submission-related documents.

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