STUDY PROTOCOL

STUDY TITLE:	A two part, fixed-sequence, open-label crossover study to evaluate potential CYP1A2-mediated drug-drug interactions of ABX464 in healthy subjects using caffeine and fluvoxamine as probe drugs.
STUDY NUMBER: *Simbec-Orion / Sponsor*	RD724/34949 / ABX464-902
EudraCT NUMBER:	2020-004879-40
IRAS ID:	290513
INVESTIGATIONAL MEDICINAL PRODUCT (IMP):	ABX464 oral capsule.
NON-INVESTIGATIONAL MEDICAL PRODUCT(s) (NIMP(s)):	caffeine oral tablets, fluvoxamine oral tablets.
PLANNED STUDY DOSE:	Part A ABX464: 50 mg once daily for 14 days Caffeine: 50 mg single dose on 3 separate occasions. Part B ABX464: 50 mg single dose on 2 separate occasions Fluvoxamine: 100 mg once daily for 10 days followed by tapering period of 50 mg for 7 days then 25 mg for 7 days.
PRINCIPAL INVESTIGATOR:	Dr Annelize Koch Simbec-Orion Clinical Pharmacology, Merthyr Tydfil Industrial Park, Pentrebach, Merthyr Tydfil, CF48 4DR, United Kingdom (UK).
STUDY SPONSOR:	ABIVAX S.A., 5 rue de la Baume, FR-75008 Paris, France.

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PROTOCOL FINALISATION STATEMENT

This protocol is not considered final unless accompanied by an approval letter from the Research Ethics Committees and Notice of Acceptance from the relevant Competent Authority.

Protocol Prepared by: SH / KS

1 SIGNATURE PAGE

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). Any changes in procedure will only be made if necessary, to protect the safety, rights or welfare of the subjects.

STUDY SPONSOR:

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2 PROTOCOL AMENDMENT/REVISION HISTORY

Protocol Version/ Date	Type of Amendment	Amendment Rationale	Sections Affected	Summary of Amendment / Changes to the Protocol
V1.0 (16-Oct-2020)	N/A	N/A	N/A	Initial version
V2.0 (20-Oct-2020)	N/A	Correction to typographical error, reduction to blood and urine safety sampling and clarification of NIMP information throughout.	Section 3: Synopsis – Methodology & Section 10.1.1: Part A – Evaluation of CYP1A2 inhibition and induction potential by ABX464 Table 10.7.1: Study Flow Chart – Part A & Table 10.7.3: Part A: Summary of Blood Volume Section 8.6: Clinical Experience & Section 12: References	Caffeine dosage strength updated on pages 6 and 28. Blood and urine safety sampling have been reduced to Day 3, Day 6, Day 9, Day 12, Day 16, Day 19 and at the post-study follow-up visit. Change of caffeine SmPC reference to PIL (or equivalent).
V3.0 (05-Nov-2020)	N/A	Response to MHRA Grounds for Non-Acceptance (GNA)	Section 3: Synopsis – Exclusion Criteria & Section 10.4.2: Exclusion Criteria Section 10.4.3: Removal of Subjects from Therapy or Assessment Section 10.6.10: Prior and	Exclusion criteria 3, 7 and 10 have been updated in line with the MHRA GNA points. Addition of pregnancy as criteria. Prior Medication section has been updated. The

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			Concomitant Therapy	following text has been removed – *unless in the opinion of the Investigator and Sponsor's Responsible Physician the medication will not interfere with the study procedures or compromise subject safety.* The following text has been added – *with the exception of paracetamol (which may be taken as an analgesic to a maximum of 2 g in 24 h [500 mg 4 times a day]).*
V4.0 (18-Nov-2020)	Non-substantial	Administrative changes and clarifications throughout.	Section 3: Synopsis – Methodology & IMP Administration, 10.1.2: Part B – Evaluation of ABX464 as a substrate for CYP1A2 & Table 10.7.2: Study Flow Chart – Part B	Revision of text for Part B to note that following administration fluvoxamine on Day 12, subjects will return to the clinical unit each morning for daily administration of fluvoxamine for 4 days (Days 13-16). Additional clarity added to confirm that all fluvoxamine doses from Day 16 onwards will be taken at home by participants until Day 25 and removal of follow up phone calls on Days 13 & 15 as these are physical visits to the clinical unit.
			Section 3: Synopsis – IMP Administration & Section 10.6.4: Administration	Clarification added to section to reference the procedure for the fluvoxamine tapering period and to clarify that the requirement to remain upright for 4 hours after dose administration applies to the ABX464

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				doses in both study Part A and study Part B.
			Section 10.5.3.2: Fluid Intake	Revision of fluid intake restriction to add clarity that fluid restriction includes not only the water taken with the dose but also any fluids consumed as part of the standardized breakfast, participants will eat prior to dose administration.
			Table 10.7.1: Study Flow Chart – Part A & Table 10.7.2: Study Flow Chart – Part B	Footnotes added and/or expanded on to detail timepoints for performing vital signs and ECGs.
			Section 10.7.1.4.3: Other Safety Assessments & Appendix 1	Removal of reference to temperature as part of vital signs assessments to align with proposed vital sign assessments schedule.
			Table 10.8.1: Summary of Source Documentation Location	Participant dosing diary added to source documentation location table.
			Section 10.9.1.3.1: Demographic and Background Data	Race has been removed as part of demographics to align with proposed demographics collected for this study.
			Section 12: References	Reference list revised to reference current approved version of IB rather than referencing the specific version.

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V5.0 (15-Dec-2020)	Non-substantial	Clarifications throughout	Section 3: Synopsis & Section 10.6.4: Administration	Update to IMP administration section to clarify that subjects only need to remain in an upright position for 4 hours following administration of caffeine doses on Day 1, Day 4 & Day 17.
			Section 10.4.1: Inclusion Criteria	Removal of 'average' from inclusion criterion #10 in relation to PR interval.
			Section 10.5.1: Contraception	Section text updated to remove reference to '2 effective methods' and revised to a 'highly effective method in addition to a condom'. Removal of list of effective methods of contraception. Addition of further language to detail requirements for males with partners of childbearing potential.
			Section 10.5.3.1: Mealtimes/Fasts	Removal of text in relation to fasting requirements for insulin and lipid profile tests.
			Section 10.7.1: Efficacy and Safety Measurements Assessed and Flow Chart	Update to PK sampling deviation window to clarify that a ± window of 1 minute applies to the PK samples up to the 45-minute timepoint.
			Table 10.7.1: Study Flow Chart – Part A & Table 10.7.2: Study	Footnotes added in both schedules to clarify timings for assessments on Day 16 (Part A) & Day 10 (Part B).

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			Flow Chart – Part B Protocol Section 10.7.1.4.3: Other Safety Assessments Appendix 1: Normal Ranges for Vital Signs and ECG Parameters Appendix 1: Normal Ranges for Vital Signs and ECG Parameters	ECG section updated to remove reference to documentation of subject initials and date of birth; text updated to reflect use of subject screening/subject number and year of birth to be recorded on ECG printouts. Update to upper range for pulse/heart rate from 100 bpm to 90 bpm as per inclusion criteria. Update to upper range for QTcF intervals for males and females from 430 msec to 450 msec for males and from 450 msec to 470 msec for females as per inclusion criteria.
V6.0 (09-Mar-2021)	Non-substantial	Management of COVID-19 vaccine deployment for ongoing non-COVID-19 clinical trials Administrative updates and clarifications throughout.	Section 3: Synopsis Section 8.7: Coronavirus Disease 2019 (COVID-19) Risk/Benefit Assessment	Updated with minor modification to planned clinical phase dates from December 2020 to April 2021 to February 2021 to May 2021 and correction of Part B methodology to note return visits for fluvoxamine administration on Day 3-10 rather than Days 2-10. COVID-19 risk/benefit section updated to reflect MHRA guidance issued in relation to the concomitant administration of COVID-19 vaccines

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				during the course of the study.
			Section 10.1: Overall Study Design and Plan	Updated with minor modification to planned clinical phase dates from December 2020 to April 2021 to February 2021 to May 2021 and correction of Part B methodology to note return visits for fluvoxamine administration on Day 3-10 rather than Days 2-10.
			Section 10.7.1.4.3: Other Safety Assessments	ECG text updated to replace reference to randomisation number with subject number.
			Section 10.7.4.1: Pharmacokinetic Blood Sampling	Section text updated to include reference to sample handling manual.

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3 SYNOPSIS

NAME OF COMPANY: ABIVAX S.A.

NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP): ABX464

NAME OF NON-INVESTIGATIONAL MEDICINAL PRODUCTS (NIMP(S)): caffeine, fluvoxamine

NAME OF ACTIVE INGREDIENT: ABX464

TITLE OF STUDY: A 2 part, fixed-sequence, open-label crossover study to evaluate potential CYP1A2-mediated drug-drug interactions of ABX464 in healthy subjects using caffeine and fluvoxamine as probe drugs.

PRINCIPAL INVESTIGATOR: Dr Annelize Koch

STUDY CENTRE: Simbec-Orion Clinical Pharmacology
Merthyr Tydfil, CF48 4DR, UK

CLINICAL PHASE: I

OBJECTIVES:

Primary

Part A:

- Evaluate the potential for inhibition and/or induction of cytochrome P450 1A2 (CYP1A2) in vivo based on the pharmacokinetics (PK) of caffeine (a known CYP1A2 substrate) in the presence and absence of ABX464.

Part B:

- Evaluate whether ABX464 is a substrate for CYP1A2 in vivo based on its PK in the presence and absence of fluvoxamine.

Secondary

Parts A & B

- Evaluate the safety and tolerability of ABX464 alone and in the presence of caffeine or fluvoxamine.

METHODOLOGY:

This is a Phase 1, 2 part, fixed-sequence open-label, crossover study to evaluate the potential CYP1A2-mediated drug-drug interactions (DDI), safety, and tolerability of ABX464 combined with a known CYP1A2 substrate (caffeine) and a known CYP1A2 inhibitor (fluvoxamine). Sixty (60) healthy adult male and female subjects 18 to 55 years of age are planned to participate in the study. Separate cohorts of subjects will be enrolled for Part A (24 subjects) and Part B (36 subjects).

The clinical phase is anticipated to take place between February 2021 and May 2021. The conclusion of the study is defined as last subject last visit.

The study will take place in the Clinical Unit of Simbec-Orion under full medical and nursing supervision.

Part A – Evaluation of CYP1A2 inhibition and induction potential by ABX464

Using a fixed-sequence crossover study design, the PK of caffeine (50 milligrams (mg) single oral dose) will be evaluated in the absence and presence of ABX464 (50 mg once daily for 14 days) in 24 healthy subjects. Caffeine will be administered on Day 1 in the absence of ABX464, on Day 4 simultaneously with ABX464 to evaluate potential CYP1A2 inhibition by ABX464, and on Day 17 simultaneously with ABX464 following 14 days of once daily dosing of ABX464 to evaluate potential CYP1A2 induction by ABX464.

Part A of the study will comprise of a pre-study screen, followed by 1 treatment period and a post-study follow-up.

Screening (Day -28 to Day -2): Screening assessments will be carried out within 28 days before first administration of NIMP. Eligible subjects will be asked to return for the treatment periods. Continued eligibility will be confirmed pre-dose during each treatment period.

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Treatment Period (Day -1 to Day 19): Eligible subjects will receive a single dose of 50 mg caffeine on three separate occasions (Days 1, 4 and 17), and multiple doses of 50 mg ABX464 once daily for 14 days (Days 4 to 17).

- **IMP:** 50 mg ABX464 oral capsules once daily for 14 days
- **NIMP:** single dose of 50 mg caffeine oral tablets on three separate occasions

The treatment period will be approximately 20 days duration, from the morning before dosing (Day -1) until 48 hours (h) post Day 17 caffeine/ABX464 dose (Day 19). Subjects will arrive at the Clinical Unit on Day -1 and will be discharged 48 h post Day 4 caffeine dose (Day 6). Subjects will return to the Clinical Unit each morning for daily administration of ABX464 (Days 7-16), and then will return to the Clinical Unit on the afternoon of Day 16. Subjects will remain in the Clinical Unit until 48 h post Day 17 caffeine/ABX464 dose (Day 19). PK samples will be collected pre-dose and up to 48 h post-dose following each administration of caffeine (15 samples per profile, total of 45 PK samples over the study) for the measurement of caffeine and its metabolite, paraxanthine. Safety will also be evaluated at specified times.

Post Study: Post-study assessments will be conducted 10 to 14 days after last dose of ABX464/caffeine on Day 17.

A schedule of all study assessments for Part A is provided in Table 10.7.1.

Part B – Evaluation of ABX464 as a substrate for CYP1A2
Using a fixed-sequence crossover study design, the PK of ABX464 (50 mg single oral dose) will be evaluated in the absence and presence of fluvoxamine (100 mg once daily for 10 days) in 36 healthy subjects. ABX464 will be administered on Day 1 in the absence of fluvoxamine and on Day 11 simultaneously with fluvoxamine following 10 days of once daily dosing of fluvoxamine to evaluate whether ABX464 is a substrate for CYP1A2.

Part B of the study will comprise of a pre-study screen, followed by 1 treatment period and a post-study follow-up.

Screening (Day -28 to Day -2): Screening assessments will be carried out within 28 days before first administration of IMP. Eligible subjects will be asked to return for the treatment periods. Continued eligibility will be confirmed pre-dose during each treatment period.

Treatment Period (Day -1 to Day 25): Eligible subjects will receive a single dose of 50 mg ABX464 on two separate occasions (Days 1 and 11), and multiple doses of 100 mg fluvoxamine. Fluvoxamine will be administered once daily for 10 days (Days 2 to 11) to investigate the effect of CYP1A2 inhibition on the PK of ABX464, followed by a tapering period to prevent fluvoxamine withdrawal effects. The tapering period will consist of 50 mg of fluvoxamine once daily for 7 days, followed by 25 mg once daily for 7 days.

- **IMP:** single dose 50 mg ABX464 oral capsules on two separate occasions
- **NIMP:** 100 mg once daily for 10 days, then tapering period of 50 mg once daily for 7 days, followed by 25 mg once daily for 7 days.

The treatment period will be approximately 26 days duration (including a fluvoxamine tapering period of 14 days), from the morning before dosing (Day -1) until the final taper dose of 25 mg fluvoxamine (Day 25). Subjects will arrive at the Clinical Unit on Day -1 and will be discharged 24 h post-Day 1 ABX464 dose (Day 2). Subjects will return to the Clinical Unit each morning for daily administration of fluvoxamine (Days 3-10), and then will return to the Clinical Unit on the afternoon of Day 10. Subjects will remain in the Clinical Unit until 24 h post-Day 11 ABX464 dose (Day 12). Following the first fluvoxamine tapering dose administration of 50 mg on Day 12, subjects will return to the Clinical Unit each morning for daily administration of fluvoxamine for 4 days (Days 13-16). This will be followed by a self-administered home dosing fluvoxamine tapering period of 50 mg for 2 days (Day 17-18) then 25 mg for 7 days (Days 19-25).

Follow-up phone calls to check fluvoxamine withdrawal symptoms: Days 17, 20, 23 and 26.

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PK samples will be collected pre-dose and up to 12 h post-dose following each administration of ABX464 (15 samples per profile, total of 30 PK samples over the study) for the measurement of ABX464 and its metabolite, ABX464-N-Glu. Safety will also be evaluated at specified times.

Post Study: Post-study assessments will be conducted 3 to 5 days after last dose of fluvoxamine on Day 25.

A schedule of all study assessments for Part B is provided in Table 10.7.2.

NUMBER OF SUBJECTS:

Part A: 24 subjects will be enrolled for 22 to complete.

Part B: 36 subjects will be enrolled for 32 to complete.

Total: 60 subjects will be enrolled for 54 to complete.

MAIN INCLUSION CRITERIA:

1. Healthy, male or female subject, between 18 and 55 years of age, inclusive.
2. Women of childbearing potential (WOCBP) and men receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 6 months (180 days) after end of study or early termination. Contraception should be in place at least 2 weeks prior to the screening visit. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. WOCBP will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception aiming at inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the subject. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle. Female and male subjects must not be planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male subjects should use a condom during the trial and for 6 months (180 days) post completion of their participation in the study. Male subjects must not donate sperm as long as contraception is required. For the purpose of this protocol, a WOCBP is any volunteer considered to be fertile, i.e. between menarche and the menopause, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Finally, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
3. Subject with a body mass index (BMI) of 18.5-30 kilogrammes per square metre (kg/m^2).
4. No clinically significant history of previous allergy / sensitivity to ABX464 or any of the excipients within the IMP.
5. No clinically significant history of previous allergy / sensitivity to caffeine (for Part A) or fluvoxamine (for Part B), or any of the excipients contained within the NIMP.
6. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP/NIMP.
7. Subject with a negative urinary drugs of abuse (DOA) screen (including alcohol and cotinine) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive result may be repeated at the Investigator's discretion).
8. Subject with negative human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg)) and hepatitis C virus antibody (HCV Ab) results at Screening.

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9. No known history of hypertension or abnormal vital signs at screening defined as supine systolic blood pressure (SBP) < 90 or > 140 millimetres of mercury (mmHg), and pulse rate < 40 or > 90 beats per minute (bpm).
10. No clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days before first dose of IMP including PR > 220 milliseconds (ms) and QT interval corrected using Fridericia formula (QTcF) >450 ms in males or >470 ms in females, or evidence of clinically significant dysrhythmias (long QT features on ECG, left bundle branch block, or ventricular arrhythmia), atrial fibrillation or history of familial long QT syndromes (Note: partial right bundle branch block is acceptable).
11. Subject must be available to complete the study (including all follow up visits/phone call).
12. Subject must satisfy an Investigator about their fitness to participate in the study.
13. Subject must provide written informed consent to participate in the study.

MAIN EXCLUSION CRITERIA:

1. Female subject who is pregnant, currently lactating or breastfeeding.
2. A clinically significant history of gastrointestinal disorder likely to influence IMP absorption.
3. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements, or any product known to interact with CYP1A2 within 28 days or 5 half-lives (whichever is longer) prior to the first dose of IMP.
4. Subject who has, or who have a relevant history of any clinically significant: neurological, gastrointestinal, renal, hepatic, cardiovascular, vascular, psychiatric, respiratory, metabolic, endocrine, or haematological conditions and/or other significant medical conditions including, without limitation, those pertaining to coronavirus disease 2019 (COVID-19) that, in the opinion of the Investigator or their appropriately qualified designee, would jeopardise the safety of the subject, safety of anyone involved in the study or impact on the validity of the study results.
5. A clinically significant history of drug or alcohol abuse (defined as the consumption of more than 14 units for male and female subjects) of alcohol a week) within the past two years.
6. Inability to communicate well with the Investigators (*i.e.*, language problem, poor mental development or impaired cerebral function).
7. Participation in a New Chemical Entity (NCE) clinical study within 3 months or five half-lives, whichever is longer, or a marketed drug clinical study within 30 days or five half-lives, whichever is longer, before the first dose of IMP (Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
8. Donation of 450 millilitres (mL) or more blood within the 3 months before the first dose of IMP.
9. Users of nicotine products *i.e.*, current smokers or ex-smokers who have smoked within 6 months prior to first dose administration with the study medication or users of cigarette replacements (*i.e.*, e-cigarettes, nicotine patches or gums).
10. Total serum bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST) / serum glutamic-oxaloacetic transaminase (SGOT) and alanine transaminase (ALT) / Serum glutamic pyruvic transaminase (SGPT) > 1.5 x upper limit of normal (ULN).
11. Experiences regular headaches (*i.e.*, experiences headaches more than weekly).

Part B Only:

12. Meets Diagnostic and Statistical Manual of Mental Disorders (5th Edition) criteria for moderate or severe substance use disorder within 6 months before Screening.

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13. Reports having experienced suicidal ideation (Type 4 or 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS]) within 30 days prior to Screening, any suicidal behaviour within 2 years prior to Screening (Any "Yes" answers on Suicidal Behaviour section of C-SSRS), and/or the Investigator assesses the subject to be a safety risk to him/herself or others;
14. Clinically significant history of depression or anxiety.

IMP ADMINISTRATION:

In Part A, each subject will receive the following IMPs & NIMPs:

- **Test IMP:** a single dose of ABX464 50 mg oral capsule will be administered once daily on Days 4 to 17.
- **NIMP:** a single dose of caffeine 50 mg oral tablet will be administered on Day 1, 4 and 17.

In Part B, each subject will receive the following IMPs & NIMPs:

- **Test IMP:** a single dose of ABX464 50 mg oral capsule will be administered on 2 separate occasions on Days 1 and 11.
- **NIMP:** a single dose of fluvoxamine 100 mg oral tablet will be administered once daily on Days 2 to 11 followed by a fluvoxamine tapering period of 50 mg for 7 days and then 25 mg for 7 days.

The IMP and NIMP will be administered within 30 minutes (mins) of a standardised breakfast with 240 mL water. Subjects must remain seating upright for at least 4 h after every administration of caffeine (Part A) i.e. Day 1, 4 & 17.

STUDY VARIABLES/ENDPOINTS:

Primary

Part A: PK parameters C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ for caffeine
Part B: PK Parameters C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ for ABX464

Secondary

Parts A & B

Secondary pharmacokinetic endpoints:

For ABX464-N-Glu and paraxanthine: C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$

For all analytes: T_{max}, λ_z, $t_{1/2}$, CL/F, Vz/F

Safety endpoints:

- Adverse Events (AEs).
- Laboratory safety tests (biochemistry, haematology, coagulation and urinalysis).
- Vital signs (systolic/diastolic blood pressure, pulse rate).
- 12-lead ECG (heart rate, RR interval, PR interval, QRS duration, QT interval and QTcF interval).

STATISTICAL METHODS:

Detailed statistical methods will be described in a separate statistical analysis plan (SAP).

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Pharmacokinetic Data

Concentration-Time Data: Individual plasma caffeine/paraxanthine (Part A) and ABX464/ABX464-N-Glu (Part B) concentration-time data will be listed. Concentration-time data will also be summarised. The descriptive statistics presented will be number of subjects in the analysis population (N), number of subjects with non-missing observations (n), arithmetic mean, geometric mean, standard deviation (SD), coefficient of variation (CV%), minimum, median and maximum. Individual and mean concentration-time data will also be plotted on both linear and semi-logarithmic scales.

For the purposes of summarizing and plotting concentration-time data, concentration value(s) below the lower limit of quantification (LLOQ) will be assigned a value of zero if the timepoint is prior to treatment and LLOQ/2 otherwise.

Derived PK Data: PK parameters will be derived from plasma caffeine/paraxanthine (Part A) and ABX464/ABX464-N-Glu (Part B) concentration-time data following administration of each NIMP/IMP using Phoenix WinNonlin (the most up to date version will be used and this will be documented in the SAP).

For the purposes of calculating PK parameters, concentration value(s) below the LLOQ will be assigned a value of zero.

Derived PK endpoints will be listed along with the points used to calculate elimination rate constant (λ_z) (lower, upper and number used) and R^2 adjusted. The derived PK endpoints will also be summarised. The descriptive statistics presented will be N, n, mean, SD, CV%, minimum, median, maximum and geometric mean (with the exception of the time to maximum plasma concentration (C_{max}; T_{max}).

Statistical analysis of the derived pharmacokinetic parameters to help understand the DDI potential for ABX464 to inhibit, induce, or be a substrate for CYP1A2, will be performed using the PK Set. The primary pharmacokinetic endpoints of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} will be log-transformed and analysed using an analysis of variance (ANOVA) model including fixed effects for treatment and subject. Point estimates and 90% confidence intervals (CIs) will be constructed for the contrasts of:

Part A

- caffeine alone on Day 1 versus caffeine dosed simultaneously with ABX464 on Day 4.
- caffeine alone on Day 1 versus caffeine dosed simultaneously with ABX464 on Day 17 following 14 days of daily dosing of ABX464.

Part B

- ABX464 alone on Day 1 versus ABX464 dosed simultaneously with fluvoxamine on Day 11 following 10 days of daily dosing of fluvoxamine.

These estimates will then be back-transformed to provide estimates of the ratios of the geometric LSMeans and corresponding 90% confidence intervals.

Safety Data

All safety data will be listed, in addition:

AEs: All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (the most up to date version that is available at the time of database build will be used and will be listed in the Data Management Plan (DMP)). The MedDRA dictionary will not be updated during the course of the study.

Laboratory Safety: Biochemistry, haematology, coagulation and urinalysis parameters will be listed with any out of normal range values flagged. Laboratory test results which are out of normal range will also be presented separately along with normal reference ranges. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day -1) values at each time-point will be tabulated.

Vital Signs: Vital signs parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day 1 pre-dose) values at each time-point will be tabulated.

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12-Lead ECG: 12-Lead ECG parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day 1 pre-dose) values at each time-point will be tabulated.	
DURATION OF STUDY:	Approximately 9 weeks for each individual (from screening to post-study follow-up).

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5 ABBREVIATIONS USED IN THE TEXT

- ABPI — Association of the British Pharmaceutical Industry
- ADL — Activities of Living
- AE(s) — adverse event(s)
- ALP — alkaline phosphatase
- ALT — alanine transaminase
- ANOVA — Analysis of variance
- aPTT — activated partial thromboplastin time
- AST — aspartate transaminase
- AUC — area under the concentration versus time curve
- $AUC_{0\text{-}inf}$ — AUC extrapolated to infinity from dosing time, based on the last measurable concentration
- $AUC_{0\text{-}t}$ — AUC from the time of dosing to the time of the last measurable concentration
- $AUC_{\%\ extrapolated}$ — residual area
- BIA — BioIndustry Association
- BMI — body mass index
- bpm — beat(s) per minute
- C_{max} — maximum plasma concentration
- Ca — calcium
- CBC — Cap Binding Complex
- CBP20 — Nuclear cap-binding protein subunit 2
- CBP80 — Nuclear cap-binding protein subunit 1
- CCRA — Clinical Contract Research Association
- CFR — Code of Federal Regulations
- CI — confidence interval
- CK — creatine kinase
- Cl — chloride
- CL/F — clearance
- CNS — central nervous system
- COVID-19 — coronavirus disease 2019
- CRF — case report form
- CRP — c-reactive protein
- C-SSRS — Columbia-Suicide Severity Rating Scale
- CTC-AE — Common Terminology Criteria for AEs
- CV% — coefficient of variation
- CYP — cytochrome
- CYP1A — cytochrome P450 1A
- CYP1A2 — cytochrome P450 1A2
- ºC — degrees Celsius
- DMP — data management plan
- DNA — Deoxyribonucleic acid
- DOA — drugs of abuse
- EC — European Commission
- EU — European Union
- eCRF — electronic case report form
- ECG — electrocardiogram
- EDTA — ethylenediaminetetraacetic acid
- EMA — European Medicines Agency
- FSH — follicle stimulating hormone
- g — gramme(s)
- GCP — Good Clinical Practice
- GDPR — General Data Protection Regulation
- GGT — gamma glutamyltransferase
- h — hour(s)
- HBsAg — hepatitis B surface antigen
- HCV Ab — hepatitis C virus antibody
- HCO_3 — bicarbonate
- HbA1c — haemoglobin A1c or glycated haemoglobin
- HIV — human immunodeficiency virus
- HRA — Health Research Authority
- IB — Investigator's Brochure
- IBD — inflammatory bowel diseases
- ICF — informed consent form
- ICH — International Council on Harmonisation

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- IMP investigational medicinal product(s)
- INR international normalised ratio
- ISF Investigator site file
- IUD intrauterine device(s)
- IUS intrauterine system
- K potassium
- kg kilogramme(s)
- kg/m^2 kilogrammes per square metre
- k_{el} elimination rate constant
- λ_z elimination rate constant
- LC MS/MS liquid chromatography tandem mass spectrometry
- LLOQ lower limit of quantification
- Ltd Limited
- M molarity
- MCH mean corpuscular haemoglobin
- MCHC mean corpuscular haemoglobin concentration
- MCP-1 monocyte chemoattractant protein-1
- MCV mean corpuscular volume
- MedDRA Medical Dictionary for Regulatory Activities
- MHRA Medicines and Healthcare products Regulatory Agency
- mg/kg milligrammes per kilogramme
- mg milligrammes
- (miR)-124 micro-RNA
- min minute
- mL millilitre
- mmHg millimetre(s) of mercury
- ms millisecond(s)
- N number dosed
- n number of observations
- Na sodium
- NCE new chemical entity
- NIMP Non-Investigational Medicinal Product
- NRES National Research Ethics Service
- QA Quality Assurance
- OCD Obsessive Compulsive Disorder
- PBMC peripheral blood mononuclear cells
- PCH Prince Charles Hospital
- PIL patient information leaflet
- PK pharmacokinetic
- PT prothrombin time
- PR interval time the electrical impulse takes to travel from the sinus node through the AV node and entering the ventricles; measured from the beginning of the P wave to the beginning of the QRS complex
- PV pharmacovigilance
- QP qualified person
- QRS QRS complex represents ventricular depolarisation
- QT interval the time for both ventricular depolarisation and repolarisation to occur, and therefore roughly estimates the duration of an average ventricular action potential.
- QTc corrected QT interval
- QTcF corrected QT interval using Fridericia's formula
- RA rheumatoid arthritis
- RBC red blood cell(s)
- RDW red blood cell distribution width
- REC Research Ethics Committee
- RNA Ribonucleic acid
- RT-PCR real-time reverse transcription polymerase chain reaction
- SAE serious adverse event
- SAP statistical analysis plan
- SAS statistical analysis software by SAS Institute Inc., USA
- SBP systolic blood pressure
- SD standard deviation
- SG specific gravity

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- SGOT serum glutamic oxaloacetic transaminase
- SGPT serum glutamic-pyruvic transaminase
- SI Statutory Instruments
- SmPC Summary of Product Characteristics
- SOC system organ class
- SOP standard operating procedure(s)
- STAT-3 signal transducer and activators of transcription
- SUSAR suspected unexpected serious adverse reaction
- $t_{½}$ terminal elimination half-life
- TEAE treatment emergent adverse event
- T_{max} the time to C_{max}
- THC tetrahydrocannabinoids
- TMF Trial Master File
- TNFα tumour necrosis factor
- UK United Kingdom
- UC Ulcerative Colitis
- UGT1A9 Uridine diphosphate Glucuronosyltransferase Family 1 Member A9
- US United States
- Vz/F volume of distribution
- WBC white blood cell(s)
- WOCBP woman (or women) of childbearing potential

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6 ETHICS

6.1 Research Ethics Committee or Institutional Review Board

This study protocol will be submitted to the Research Ethics Committee (REC) for review and provision of a favourable opinion. The favourable opinion of the REC must be obtained before commencement of any study procedures.

The favourable opinion is conditional upon the Sponsor registering the clinical trial in a publicly accessible database, within 6 weeks of the first participant recruited or following confirmation of an appropriate Health Research Authority (HRA) deferral.

All substantial protocol amendments must receive favourable opinion from the REC responsible for the study. Non-substantial amendments will not require prior favourable opinion by the REC.

If the study is stopped due to adverse events (AEs) it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (*e.g.,* completed) will be reported to the REC responsible for the study within 90 days of completion of the last subject's final study procedures. In the event of the study being prematurely terminated a summary safety report will be submitted to the REC responsible for the study within 15 days.

A summary of the clinical study report will be submitted to the REC responsible for the study within 1 year of completion of the last subject's final study procedures.

The REC will be informed that Simbec-Orion is a commercial organisation and that the study is funded by ABIVAX S.A. The subjects who take part in the clinical study will be paid for their inconvenience and have been informed that there will be no benefits gained by their participation. All potential conflicts of interest will be declared by the Investigators.

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6.2 Ethical Conduct of the Study

The Principal Investigator shall be responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki (Brazil 2013). It will comply with International Council on Harmonisation (ICH) Good Clinical Practice (GCP)[1] and applicable regulatory requirements.

6.3 Subject Information and Consent

Potential subjects who volunteer for participation in the study will be informed of the aims, methods, anticipated benefits and potential hazards of the study and any possible discomfort it may entail. Information will be given in both oral and written form and in the manner deemed appropriate by the Clinical Unit standard operating procedures (SOPs). Each subject will also be informed of his/her right to withdraw from the study at any time, for any reason.

A written explanation (participant information sheet) and informed consent form (ICF) will be provided and the subject will be allowed sufficient time to consider the study information. Prior to signing the ICF, the subject will be given an opportunity to discuss any issues concerning the study with an Investigator who has suitable knowledge of the study and will have all questions answered openly and honestly.

If the subject is willing to participate in the study, the ICF will be signed and personally dated by the subject and the person taking consent. The subject will receive a copy of the ICF together with the participant information sheet and the original signed ICF will be retained with the study records at the Investigator site. In addition, the actions and completion of the consenting process will be recorded in the subject's medical record (*i.e.*, source document).

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7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study will be performed at a single site, Simbec-Orion Clinical Pharmacology Unit. The overall responsibility for the study will rest with the Principal Investigator, Dr Annelize Koch. The Project Manager will act on behalf of the Principal Investigator to ensure the smooth and efficient running of all aspects of the study.

7.1 Study Personnel

Contract Research Organisation: Simbec-Orion

Principal Investigator:	Dr Annelize Koch
Project Manager (Main Contact):	Kiren Sidhu
Project Manager Deputy:	Jack Lippitt
Pharmacokinetics (PK):	Dr Simon Hutchings
Statistics:	Kerry Williams
Data Management:	Seshu Kanneganti
Laboratory Services:	Sara Howell
IMP Management:	Dr Rebecca Price-Davies

The Principal Investigator will delegate study-related activities according to staff responsibilities and job descriptions. This will be documented in a study-specific delegation of responsibilities form.

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Sponsor: ABIVAX S.A.

Project Manager (Main Contact):	Pascaline Ploncard
Sponsor's Responsible Physician:	Jean-Marc Steens

Monitoring: Simbec-Orion Clinical Development

Pharmacovigilance (PV): IntuVigilance Ltd

7.2 Indemnity Arrangements

The Sponsor and Simbec-Orion carry insurance to pay compensation for injury, accident, ill health or death caused by participation in this study without regard to proof of negligence in accordance with the insurance and compensation in the event of injury in phase I clinical trials 2012, guidance issued by the Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA) and the Clinical Contract Research Association (CCRA) in consultation with the Department of Health and the National Research Ethics Service (NRES).

8 INTRODUCTION

8.1 Background information

ABX464 is a first-in-class, orally available, small molecule with anti-inflammatory activity which is under investigation as a potential treatment for inflammatory conditions including ulcerative colitis (UC) and rheumatoid arthritis (RA). ABX464 binds the Cap Binding Complex (CBC) comprised of two proteins Nuclear cap-binding protein subunit 2 (CBP20) and Nuclear cap-binding protein subunit 2 (CBP80), within the cell nucleus. This binding leads to an increased expression of a single micro-Ribonucleic acid (RNA; miR-124) by impacting the splicing of a single long non-coding RNA. Because of its action on this single splicing event, leading to an increase in miR-124, a microRNA with potent anti-inflammatory properties, ABX464 potentially has broad applicability across a variety of inflammatory diseases including RA and inflammatory bowel diseases (IBD). ABX464, through binding to the CBC also modulates the splicing of human immunodeficiency viruses (HIV)-RNA and reduces HIV-Deoxyribonucleic acid (DNA) and potentially has utility as a functional cure for HIV infection.

8.2 Non-clinical Pharmacology

In vitro studies demonstrated that ABX464, and its main metabolite, ABX464-N-Glu, induce a significant increase in miR-124 expression in human peripheral blood mononuclear cells (PBMCs) and human monocyte-derived macrophages. Modulation of miR-124 by ABX464 may mediate a disease specific anti-inflammatory effect as miR-124 is known to inhibit translation of many inflammatory targets *i.e.*, interleukin-6 receptor, signal transducer and activators of transcription (STAT-3), monocyte chemoattractant protein-1 (MCP-1) and Tumor necrosis factor (TNFα).

8.3 Safety Pharmacology

No adverse effects were observed on the central or peripheral nervous systems or on the respiratory function after ABX464 administration up to 300 milligrammes per kilogramme (mg/kg) in wistar rats. In marmoset monkeys, ABX464 administered up to 250 mg/kg had no significant effect on arterial blood pressure, heart rate or cardiac conduction times.

8.4 Non-clinical Pharmacokinetics and product metabolism

Glucuronidation, mediated by Uridine Diphosphate Glucuronosyltransferase Family 1 Member A9 (UGT1A9), is the main metabolic pathway of ABX464 and was observed in vivo in all species studied to variable extents. ABX464 is typically absorbed within 1 to 14 (hours) h. ABX464-N-Glu is formed rapidly within a few hours with exposures usually higher than for the parent compound. Mice and non-human primates, especially the cynomolgus monkey had the highest exposure to the metabolite following ABX464 administration while rats, minipigs and dogs were the least exposed.

Oxidative metabolism via the cytochrome (CYP) P450 pathway was also identified as a route of metabolism for ABX464, with cytochrome P450 1A2 (CYP1A2) identified as the major contributing isoform. Subsequent studies also demonstrated that ABX464 was a strong inhibitor of CYP1A2 in human liver microsomes and induced its expression in human hepatocytes. Following repeated administrations of ABX464, a reversible induction of

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cytochrome P450 1A (CYP1A) was observed in rat (male) and in dog liver microsomes (both female and male). These findings indicate a potential clinically significant interaction with co-administered CYP1A2 substrates and are the basis for this clinical study to evaluate potential CYP1A2-mediated drug interactions.

Plasma exposure of ABX464 saturated at approximately 20, 40 and 75 mg/kg in dogs, rats and marmoset monkeys, respectively. A decrease in systemic exposure upon repeated, daily dosing was observed in rats, dogs and minipigs.

No significant differences were found between genders.

ABX464 and ABX464-N-Glu are highly bound to proteins (93 to > 99% bound fraction) in non-human primate (tested for ABX464 only), rodent, dog, and human plasma.

8.5 Toxicology

The toxicity of repeated-doses of ABX464 was assessed in wistar rats, cynomolgus and marmoset monkeys, göttingen minipigs and beagle dogs with treatment durations ranging from 2-weeks to 6/9 months. In these studies, the main target organs of ABX464 toxicity were the gastro-intestinal tract and the liver, with ptyalism, vomiting, body weight losses as the main findings. The main microscopic findings observed in these organs were dark foci in the glandular mucosa of stomach, adverse altered cell foci and bile duct hyperplasia in the liver, adverse erosion/ulcer in the forestomach, centrilobular hepatocellular degeneration/necrosis and liver necrosis. ABX464-N-Glu was assessed in a 4-month study in marmoset monkeys. The main findings were weight loss and haematological changes, which were considered adverse only at the highest dose tested.

ABX464 and ABX464-N-Glu are non-mutagenic. In reprotoxicology studies, the main findings were external variations and malformations observed in embryo-fetal development studies suggesting a potential teratogenic effect of ABX464.

8.6 Clinical Experience

The effect of ABX464 in humans has been assessed in 5 completed clinical studies in healthy volunteers and in HIV-patients, as well as in 1 completed Phase 2a 8-week study in patients with UC (ABX464-101). In addition, 12-month efficacy and safety data are available from an interim analysis of the longer-term maintenance Phase 2a study ABX464-102 in UC. Two Phase 2b studies in UC (ABX464-103; ABX464-104) and two Phase 2a studies in RA (ABX464-301; ABX464-302) are ongoing.

As of 31 October 2019, clinical exposure to ABX464 is approaching up to two years. 211 subjects have received single doses (25 to 200 milligrams (mg)) of ABX464, or repeated doses (50 to 150 mg). Overall, the safety profile of ABX464 is good; eight serious adverse events have been reported with ABX464, which were considered not related to the investigational product. The most frequently reported AEs were nausea, vomiting and headache which were of mild to moderate intensity, occurring after treatment onset and transient in nature.

ABX464 was rapidly absorbed and metabolised into ABX464-N-Glu, within about 1 h of treatment. After repeated administrations of ABX464, an initial decrease in ABX464 area under the curve (AUC) was observed until steady state was reached after approximately 4

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weeks of treatment. Exposure to ABX464-N-Glu is much higher than to ABX464 in all patients. ABX464-N-Glu is pharmacologically active. Food increases ABX464 exposure by about 3-4-fold while exposure to ABX464-N-Glu is comparable in fed or fasted conditions.

Further details of the non-clinical studies and a summary of the known and potential risks and benefits of ABX464 can be found in the Investigator's brochure (IB)[2], patient information leaflet (PIL)[3] (or equivalent) for caffeine and summary of product characteristics (SmPC) for fluvoxamine (NIMPs)[4].

The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s), as indicated within Section 6.2.5 of the ICH GCP E6 (R2) guidelines[1].

8.7 Coronavirus Disease 2019 (COVID-19) Risk/Benefit Assessment

This study is to be conducted in healthy adult volunteers who are deemed not to be at higher risk of COVID-19 as per NHS Guidance (https://www.nhs.uk/conditions/coronavirus-covid-19/people-at-higher-risk/whos-at-higher-risk-from-coronavirus/; last reviewed 25 September 2020).

The safety of the participant is the primary concern; this study is to be conducted at Simbec-Orion Clinical Pharmacology Unit which is a Phase I accredited unit with extensive experience in conducting Phase I trials of similar design. Simbec-Orion prioritise the health and wellbeing of their clinical trial participants and, as such, have implemented a number of COVID-19 policies and risk mitigating actions. Prior to attendance at site, volunteers will be contacted to ensure they are not displaying any COVID-19 symptoms; Site COVID-19 policies will be explained to them at this time. Where appropriate perspex screens are in place and appropriate social distancing is enforced, when this is not possible, appropriate PPE will be worn.

Simbec-Orion Clinical Pharmacology unit is a dedicated trial facility and, as such, staffing levels will not be affected by the potential burden presented by COVID-19 to other medical facilities. All employees present at the clinical site are aware of the COVID-19 specific working requirements and will work to the relevant 'Working Safely' Policy.

Medicines and Healthcare products Regulatory Agency (MHRA) Phase I Accreditation requirement No. 3 details the requirement for an agreement with a local hospital for supporting emergencies arising from the clinical trials performed by Simbec-Orion, this agreement is in place with Cwm Taf University Health Board and Prince Charles Hospital (PCH) for this purpose. Cwm Taf University Health Board and PCH have confirmed capacity to support any acute serious AEs (SAEs) during the COVID-19 pandemic (details contained within Simbec-Orion Clinical General Risk Assessment_v1.0 (16 June 2020)).

The IMP is not an immunosuppressant. There is no scientific evidence that ABX464 increases a subject's susceptibility to COVID-19 or will exacerbate a subject's condition should they contract COVID-19. In addition, all subjects will remain in-house for the duration of the study, under the medical supervision of the Principal Investigator throughout.

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Both the Study and Site Risk Assessments will be continually monitored and updated throughout the trial and it is currently deemed acceptable to conduct the trial without it impacting or being impacted by the COVID-19 pandemic.

In addition, the sponsor has conducted a risk assessment in consideration of the ongoing COVID-19 vaccine deployment programme including assessment of the potential risks associated with concomitant vaccination whilst participating in this trial.

The sponsor has determined that the outcome of the risk assessment undertaken in conjunction with the study team is that a COVID-19 vaccine may be given to a trial participant during the study (including prior to enrolment up to completion of the final post-study follow up assessment) if they are invited to do so and is considered as a concomitant medication with no interaction that requires advice on timing of the vaccine or any other aspect.

Participants will be informed that they are to notify the Simbec-Orion team if they are invited to receive a COVID-19 vaccine at any point during the study so that this may be documented accordingly.

Concomitant administration of ABX464 during an ongoing round of vaccination will not, to the best extent of available knowledge, compromise the efficacy of any current approved COVID-19 vaccine or otherwise induce or exacerbate any effects of current approved COVID-19 vaccines or have any known undue interactions. The study team will continue to review and monitor any update in terms of COVID-19 vaccine interaction with medications within the relevant therapeutic class for ABX464. This will include an assessment of any further COVID-19 vaccines which receive approval for use during the course of the study.

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9 STUDY OBJECTIVES

9.1 Primary Study Objective

Part A:
Evaluate the potential for inhibition and/or induction of CYP1A2 in vivo based on the PK of caffeine (a known CYP1A2 substrate) in the presence and absence of ABX464.

Part B:
Evaluate whether ABX464 is a substrate for CYP1A2 in vivo based on its PK in the presence and absence of fluvoxamine.

9.2 Secondary Study Objective

Parts A & B

Evaluate the safety and tolerability of ABX464 alone and in the presence of caffeine or fluvoxamine.

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10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a Phase 1, 2 part, fixed-sequence open-label, crossover study to evaluate the potential CYP1A2-mediated drug-drug interactions (DDI), safety, and tolerability of ABX464 combined with a known CYP1A2 substrate (caffeine) and a known CYP1A2 inhibitor (fluvoxamine). Sixty (60) healthy adult male and female subjects 18 to 55 years of age are planned to participate in the study. Separate cohorts of subjects will be enrolled for Part A (24 subjects) and Part B (36 subjects).

The clinical phase is anticipated to take place between February 2021 and May 2021. The conclusion of the study is defined as last subject last visit.

The study will take place in the Clinical Unit of Simbec-Orion under full medical and nursing supervision.

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10.1.1 Part A – Evaluation of CYP1A2 inhibition and induction potential by ABX464

Using a fixed-sequence crossover study design, the PK of caffeine (50 mg single oral dose) will be evaluated in the absence and presence of ABX464 (50 mg once daily for 14 days) in 24 healthy subjects. Caffeine will be administered on Day 1 in the absence of ABX464, on Day 4 simultaneously with ABX464 to evaluate potential CYP1A2 inhibition by ABX464, and on Day 17 simultaneously with ABX464 following 14 days of once daily dosing of ABX464 to evaluate potential CYP1A2 induction by ABX464.

Part A of the study will comprise of a pre-study screen, followed by 1 treatment period and a post-study follow-up.

Screening (Day -28 to Day -2): Screening assessments will be carried out within 28 days before first administration of NIMP. Eligible subjects will be asked to return for the treatment periods. Continued eligibility will be confirmed pre-dose during each treatment period.

Treatment Period (Day -1 to Day 19): Eligible subjects will receive a single dose of 50 mg caffeine on three separate occasions (Days 1, 4 and 17), and multiple doses of 50 mg ABX464 once daily for 14 days (Days 4 to 17).

- **IMP:** 50 mg ABX464 oral capsules once daily for 14 days.
- **NIMP:** single dose of 50 mg caffeine oral tablets on three separate occasions.

The treatment period will be approximately 20 days duration, from the morning before dosing (Day -1) until 48 h post Day 17 caffeine/ABX464 dose (Day 19). Subjects will arrive at the Clinical Unit on Day -1 and will be discharged 48 h post Day 4 caffeine dose (Day 6). Subjects will return to the Clinical Unit each morning for daily administration of ABX464 (Days 7-16), and then will return to the Clinical Unit on the afternoon of Day 16. Subjects will remain in the Clinical Unit until 48 h post Day 17 caffeine/ABX464 dose (Day 19). PK samples will be collected pre-dose and up to 48 h post-dose following each administration of caffeine (15 samples per profile, total of 45 PK samples over the study) for the measurement of caffeine and its metabolite, paraxanthine. Safety will also be evaluated at specified times.

Post Study: Post-study assessments will be conducted 10 to 14 days after last dose of ABX464/caffeine on Day 17.

A schedule of all study assessments for Part A is provided in Table 10.7.1.

10.1.2 Part B – Evaluation of ABX464 as a substrate for CYP1A2

Using a fixed-sequence crossover study design, the PK of ABX464 (50 mg single oral dose) will be evaluated in the absence and presence of fluvoxamine (100 mg once daily for 10 days) in 36 healthy subjects. ABX464 will be administered on Day 1 in the absence of fluvoxamine and on Day 11 simultaneously with fluvoxamine following 10 days of once daily dosing of fluvoxamine to evaluate whether ABX464 is a substrate for CYP1A2.

Part B of the study will comprise of a pre-study screen, followed by 1 treatment period and a post-study follow-up.

Screening (Day -28 to Day -2): Screening assessments will be carried out within 28 days before first administration of IMP. Eligible subjects will be asked to return for the treatment periods. Continued eligibility will be confirmed pre-dose during each treatment period.

Treatment Period (Day -1 to Day 25): Eligible subjects will receive a single dose of 50 mg ABX464 on two separate occasions (Days 1 and 11), and multiple doses of 100 mg fluvoxamine. Fluvoxamine will be administered once daily for 10 days (Days 2 to 11) to investigate the effect of CYP1A2 inhibition on the PK of ABX464, followed by a tapering period to prevent fluvoxamine withdrawal effects. The tapering period will consist of 50 mg of fluvoxamine once daily for 7 days, followed by 25 mg once daily for 7 days.

- **IMP:** single dose 50 mg ABX464 oral capsules on two separate occasions.
- **NIMP:** 100 mg once daily for 10 days, then tapering period of 50 mg once daily for 7 days, followed by 25 mg once daily for 7 days.

The treatment period will be approximately 26 days duration (including a fluvoxamine tapering period of 14 days), from the morning before dosing (Day -1) until the final taper dose of 25 mg fluvoxamine (Day 25). Subjects will arrive at the Clinical Unit on Day -1 and will be discharged 24 h post-Day 1 ABX464 dose (Day 2). Subjects will return to the Clinical Unit each morning for daily administration of fluvoxamine (Days 3-10), and then will return to the Clinical Unit on the afternoon of Day 10. Subjects will remain in the Clinical Unit until 24 h post-Day 11 ABX464 dose (Day 12). Following the first fluvoxamine tapering dose administration of 50 mg on Day 12, subjects will return to the Clinical Unit each morning for daily administration of fluvoxamine for 4 days (Days 13-16). This will be followed by a self-administered home dosing fluvoxamine tapering period of 50 mg for 2 days (Day 17-18) then 25 mg for 7 days (Days 19-25).

Follow-up phone calls to check fluvoxamine withdrawal symptoms: Days 17, 20, 23 and 26.

PK samples will be collected pre-dose and up to 12 h post-dose following each administration of ABX464 (15 samples per profile, total of 30 PK samples over the study) for the measurement of ABX464 and its metabolite, ABX464-N-Glu. Safety will also be evaluated at specified times.

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Post Study: Post-study assessments will be conducted 3 to 5 days after last dose of fluvoxamine on Day 25.

A schedule of all study assessments for Part B is provided in Table 10.7.2.

10.2 Study Stopping Criteria

The study will be discontinued if any unacceptable safety findings are identified. This decision will be made jointly by the Principal Investigator (or deputy) and ABIVAX S.A. A written document signed by the Principal Investigator (or deputy) and ABIVAX S.A. will be produced ratifying the decision.

Please see Section 10.4.3 for possible reasons for discontinuation of an individual subject.

10.3 Discussion of Study Design, including the Choice of Control Groups

The study design has been chosen in accordance with the European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA) guidelines on the design, conduct and evaluation of drug interactions. In drug interaction studies, IMPs may be referred to as 'victim' drugs or 'perpetrator' drugs. The victim drug is the drug affected by the drug-drug interaction, regardless of whether it is the investigational drug or another medicinal product. The perpetrator drug is the drug which affects the PK of the other drug. Whether an IMP is considered a victim or perpetrator depends on the nature of the interaction being evaluated; as described below, in this study ABX464 is considered the perpetrator in Part A (the effect of ABX464 on the PK of caffeine is being evaluated), while in Part B ABX464 is considered the victim (the effects of fluvoxamine on the PK of ABX464 is being evaluated).

Part A

Part A of the study will be carried out in healthy subjects. Each subject will receive a single dose of 50 mg caffeine on three separate occasions (Days 1, 4 and 17), and multiple doses of 50 mg ABX464 once daily for 14 days (Days 4 to 17). In Part A of the study ABX464 is considered the 'perpetrator' drug and caffeine the 'victim' drug.

The guidance recommends that sample collection for the victim drug should be spaced in such a way that maximum plasma concentration (C_{max}) and elimination rate constant (k_{el}) can be accurately estimated. It is therefore important that there are enough sampling times clustered around C_{max}. The guidance also requires that sampling should continue for at least 3 x terminal elimination half-life ($t_{1/2}$) of the drug, and that at least 3 to 4 samples should be obtained during the terminal log-linear phase. Caffeine reaches C_{max} after approximately 0.5 and 2 h and has a plasma $t_{1/2}$ of approximately 5 h. Therefore, collecting samples up to 48 h post dose is considered appropriate. The washout period of at least 3 days between doses (longer than the required 5 x $t_{1/2}$), allows complete elimination of caffeine between each dose and is deemed sufficiently long to avoid any carry-over effect.

ABX464 will be co-administered with caffeine on two occasions; as an initial dose on Day 4, then on Day 17, following 14 days of once daily dosing of ABX464. The co-administration on Day 4 is to evaluate the potential for inhibition of CYP1A2 by the perpetrator drug (ABX464) following a single dose, while the co-administration on Day 17 is to evaluate the potential for induction of CYP1A2 by the perpetrator following multiple dosing for 14 days, which is considered an appropriate duration of dosing to obtain maximum induction of CYP isoforms.

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The dose of 50 mg ABX464 was chosen as this is anticipated as the recommended clinical dose during subsequent clinical trials. In addition, given the established significant effect of food on the PK of ABX464, all doses of ABX464 will be administered within 30 minutes (mins) of the consumption of a standardised breakfast.

As the primary objective of Part A of the study is to compare the PK of caffeine (a known CYP1A2 substrate) in the presence and absence of ABX464, an open-label design was chosen. As the PK parameters investigated are objective, it was considered that there was only minimal risk of introducing bias into the study.

The crossover design permits within-subject comparison, which results in reduced variability of the data obtained.

Caffeine was chosen as the probe victim drug for Part A as it is a well-established substrate for CYP1A2, and therefore its PK are sensitive to either inhibition or induction of CYP1A2 by a perpetrator drug. Currently caffeine is licensed over the counter in the UK as a treatment to reduce the symptoms of fatigue and tiredness[3].

Part B

Part B of the study will be carried out in healthy subjects. Each subject will receive a single dose of 50 mg ABX464 on two separate occasions (Days 1 and 11), and multiple doses of 100 mg fluvoxamine once daily for 10 days (Days 2 to 11) to investigate the effect of CYP1A2 inhibition on the PK of ABX464, followed by a tapering period to prevent withdrawal effects. In Part B of the study ABX464 is considered the victim drug and fluvoxamine the perpetrator drug.

The guidance requires that sample collection for the victim drug should be spaced in such a way that C_{max} and k_{el} can be accurately estimated. It is therefore important that there are enough sampling times clustered around C_{max}. The guidance also requires that sampling should continue for at least 3 x $t_{1/2}$ of the drug, and that at least 3 to 4 samples should be obtained during the terminal log-linear phase. ABX464 reaches C_{max} after approximately 3 h following administration with food and has a plasma $t_{1/2}$ of approximately 0.9 h. Therefore, collecting samples up to 12 h post dose is considered appropriate. The washout period of at least 10 days between doses (longer than the required 5 x $t_{1/2}$), allows complete elimination of ABX464 between each dose and is deemed sufficiently long to avoid any carry-over effect. The dose of 50 mg ABX464 was chosen as this is anticipated as the recommended clinical dose during subsequent clinical trials. In addition, given the established significant effect of food on the PK of ABX464, all doses of ABX464 will be administered within 30 mins of the consumption of a standardised breakfast.

Fluvoxamine will be co-administered with ABX464 on Day 11, following 10 days of once daily dosing of fluvoxamine. The co-administration on Day 11 is to evaluate the effect of CYP1A2 inhibition by fluvoxamine on the PK of ABX464. Based on the SmPC for fluvoxamine, steady state plasma levels should be achieved following 10 days of once-daily dosing, which is considered an appropriate to obtain maximum inhibition of CYP1A2.

As the primary objective of Part B of the study is to compare the PK of ABX464 in the presence and absence of fluvoxamine (a known CYP1A2 inhibitor), an open-label design was chosen. As the PK parameters investigated are objective, it was considered that there was only minimal risk of introducing bias into the study.

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The crossover design permits within-subject comparison, which results in reduced variability of the data obtained.

Fluvoxamine was chosen as the probe perpetrator drug for Part B as it is a well-established inhibitor of CYP1A2, and therefore its coadministration should affect the P of a victim drug that is metabolised via CYP1A2. Currently fluvoxamine is licensed in the UK for the treatment of Major depressive episode and Obsessive-Compulsive Disorder (OCD) with a recommended daily dose of 100 mg[4].

10.4 Selection of Study Population

A total of 60 subjects will be required to complete the study.

The study is to be conducted in healthy subjects and therefore participants are not expected to derive any therapeutic benefit from taking part. A healthy subject population with carefully considered inclusion/exclusion criteria will avoid the potential for interaction of ABX464 with any underlying disease state or concomitant medication that it may be necessary for patients to take, while ensuring that subjects are fit and well enough for participation in the study.

The following eligibility criteria are designed to select subjects for whom protocol treatment and procedures are considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

Deviations from inclusion and exclusion criteria are not allowed as deviations have the potential to impact the scientific integrity of the study, regulatory acceptability or participant safety as such deviations constitute a deliberate breach of Regulation 29 of Statutory Instrument (SI) 2004/1031. Therefore, adherence to the criteria as specified in the protocol is essential.

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10.4.1 Inclusion Criteria

To be confirmed at Screening (Days -28 to -2):

1. Healthy, male or female subject, between 18 and 55 years of age, inclusive.
2. Women of childbearing potential (WOCBP) and men receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 6 months (180 days) after end of study or early termination. Contraception should be in place at least 2 weeks prior to the screening visit. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. WOCBP will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception aiming at inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the subject. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle. Female and male subjects must not be

planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male subjects should use a condom during the trial and for 6 months (180 days) post completion of their participation in the study. Male subjects must not donate sperm as long as contraception is required. For the purpose of this protocol, a WOCBP is any volunteer considered to be fertile, i.e. between menarche and the menopause, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Finally, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

3. Subject with a body mass index (BMI) of 18.5-30 kg/m².
4. No clinically significant history of previous allergy / sensitivity to ABX464 or any of the excipients within the IMP.
5. No clinically significant history of previous allergy / sensitivity to caffeine (for Part A) or fluvoxamine (for Part B), or any of the excipients contained within the NIMP.
6. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP/NIMP.
7. Subject with a negative urinary drugs of abuse (DOA) screen (including alcohol and cotinine) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive result may be repeated at the Investigator's discretion).
8. Subject with negative human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg)) and hepatitis C virus antibody (HCV Ab) results at Screening.
9. No known history of hypertension or abnormal vital signs at screening defined as supine systolic blood pressure (SBP) < 90 or > 140 millimetres of mercury (mmHg), and pulse rate < 40 or > 90 beats per minute (bpm).
10. No clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days before first dose of IMP including PR > 220 milliseconds (ms) and QT interval corrected using Fridericia formula (QTcF) >450 ms in males or >470 ms in females, or evidence of clinically significant dysrhythmias (long QT features on ECG, left bundle branch block, or ventricular arrhythmia), atrial fibrillation or history of familial long QT syndromes. (Note: partial right bundle branch block is acceptable);
11. Subject must be available to complete the study (including all follow up visits/phone call).

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12. Subject must satisfy an Investigator about their fitness to participate in the study.
13. Subject must provide written informed consent to participate in the study.

To be re-confirmed on Day -1 / prior to first dose administration:

1. Subject continues to meet all screening inclusion criteria.
2. Subject with a negative urinary DOA screen (including alcohol) prior to first dose administration.
3. WOCBP Female subjects with a negative pregnancy test.

10.4.2 Exclusion Criteria

To be confirmed at Screening (Days -28 to -2):

1. Female subject who is pregnant, currently lactating or breastfeeding.
2. A clinically significant history of gastrointestinal disorder likely to influence IMP absorption.
3. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements, or any product known to interact with CYP1A2 within 28 days or 5 half-lives (whichever is longer) prior to the first dose of IMP.
4. Subject who has, or who have a relevant history of any clinically significant: neurological, gastrointestinal, renal, hepatic, cardiovascular, vascular, psychiatric, respiratory, metabolic, endocrine, or haematological conditions and/or other significant medical conditions including, without limitation, those pertaining to COVID-19 that, in the opinion of the Investigator or their appropriately qualified designee, would jeopardise the safety of the subject, safety of anyone involved in the study or impact on the validity of the study results.
5. A clinically significant history of drug or alcohol abuse (defined as the consumption of more than 14 units for male and female subjects) of alcohol a week) within the past two years.
6. Inability to communicate well with the Investigators (*i.e.*, language problem, poor mental development or impaired cerebral function).
7. Participation in a New Chemical Entity (NCE) clinical study within 3 months or five half-lives, whichever is longer, or a marketed drug clinical study within 30 days or five half-lives, whichever is longer, before the first dose of IMP (Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
8. Donation of 450 millilitres (mL) or more blood within the 3 months before the first dose of IMP.

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9. Users of nicotine products *i.e.*, current smokers or ex-smokers who have smoked within 6 months prior to first dose administration with the study medication or users of cigarette replacements (*i.e.*, e-cigarettes, nicotine patches or gums).
10. Total serum bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST) / serum glutamic-oxaloacetic transaminase (SGOT) and alanine transaminase (ALT) / Serum glutamic pyruvic transaminase (SGPT) > 1.5 x upper limit of normal (ULN).
11. Experiences regular headaches (*i.e.*, experiences headaches more than weekly).

Part B Only:

12. Meets Diagnostic and Statistical Manual of Mental Disorders (5th Edition) criteria for moderate or severe substance use disorder within 6 months before Screening.
13. Reports having experienced suicidal ideation (Type 4 or 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS]) within 30 days prior to Screening, any suicidal behaviour within 2 years prior to Screening (Any "Yes" answers on Suicidal Behaviour section of C-SSRS), and/or the investigator assesses the subject to be a safety risk to him/herself or others;
14. Clinically significant history of depression or anxiety.

To be re-confirmed at Day -1 / prior to first dose administration:

1. Development of any exclusion criteria since screening.
2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements since screening.
3. Participation in a clinical study since the screening visit.
4. Donation of 450 mL or more blood since the screening visit.

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10.4.3 Removal of Subjects from Therapy or Assessment

Each subject will be informed of their right to withdraw from the study at any time and for any reason.

An Investigator will withdraw a subject from the study at any time for any of the following reasons:

- If a subject experiences a serious or intolerable AE, that prevents them from continuing.
- If a subject incurs a significant protocol violation which impacts on their safety or the scientific integrity of the study (this will be discussed on a case-by-case basis with the sponsor).
- At the request of the Sponsor.

- If it is considered that the subject's health is compromised by remaining in the study or the subject is not sufficiently cooperative.
- If a subject is lost to follow-up.
- If a subject becomes pregnant.

The reasons for any subject withdrawal will be recorded on the study completion form of the case report form (CRF).

If a subject is withdrawn or chooses to withdraw from the study for any reason, every possible effort will be made to perform the evaluations described for the post-study follow-up (see Table 10.7.1 and Table 10.7.2). The data collected from withdrawn subjects will be included in the study report.

In the event of any abnormalities considered to be clinically significant, subjects will be followed up with appropriate medical management until values are considered to be clinically acceptable. Referral or collaborative care will be organised if considered necessary.

Twenty-two (22) subjects are required to complete Part A of the study and thirty-two (32) subjects are required to complete Part B of the study. Subjects who withdraw from the study before receiving any study medication will be replaced. Subjects who are withdrawn from the study due to significant drug-related AEs will not be replaced. Replacement of all other subjects withdrawn from the study after receiving study medication will be decided on a case-by-case basis by the Principal Investigator (or deputy) and ABIVAX S.A.

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10.5 Additional Advice for Study Population

10.5.1 Contraception

To prevent pregnancy, female subjects of childbearing potential must be willing to use a highly effective method of contraception in addition to a condom for their partner, if applicable (unless of non-childbearing potential or where abstaining from sexual intercourse was in-line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]) from at least 2 weeks prior to the screening visit and for at least 6 months (180 days) after end of study or early termination.

Male subjects (with a female partner of childbearing potential) must be willing to use a highly effective method of contraception in addition to a condom from at least 2 weeks prior to the screening visit and for at least 6 months (180 days) after end of study or early termination.

Highly effective methods of contraception include:

- Combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal and transdermal) associated with inhibition of ovulation,
- Progestogen-only hormonal contraception (oral, injectable and implantable) aiming at inhibition of ovulation,
- IUD,

- Intrauterine hormone-releasing system (IUS),
- Bilateral tubal occlusion,
- Vasectomised partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.
- True abstinence - in line with the preferred and usual lifestyle of the subject.

To prevent exposure of any partner (male or female) during non-vaginal intercourse to the semen from a male subject who has been exposed to the IMP, the following contraception must be used:

- Condom.

The chosen contraception method(s) must be followed from at least 2 weeks prior to the Screening visit and for at least 6 months (180 days) after end of study or early termination.

Male subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

10.5.2 Sperm Donation

Subjects must not donate sperm from at least 2 weeks prior to the Screening visit and for at least 6 months (180 days) after end of study or early termination.

10.5.3 Diet and Fluid Restrictions

10.5.3.1 Meal Times/Fasts

Subjects will fast overnight for at least 10 h then -

A standard breakfast will be served: 30 min pre-dose.

Lunch will be served: approximately 4 h post-dose.

Dinner will be served: approximately 8 h post-dose.

Snack will be served: approximately 12 h post-dose.

On all non-dosing study days, whilst resident in the Clinical Unit, meals will be served at standard times.

Subjects will choose meals from a standard menu while resident at the Clinical Unit.

10.5.3.2 Fluid Intake

No fluids (apart from water taken with dose and tea / coffee with breakfast) are allowed from 1 h prior to dosing with IMP and/or NIMP until 1 h afterwards. Water is then allowed *ad libitum* and at least 240 mL should be drank every 4 h during waking hours. Squash/cordial are allowed from 4 h post dose and decaffeinated tea and coffee from 8 h post dose.

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10.5.3.3 Alcohol Intake

The consumption of alcohol will be limited to a maximum of 2 units per day from 7 days prior to the first dose of NIMP/IMP. Alcohol will be avoided completely for a period of not less than 2 days prior to the first dose of NIMP/IMP and throughout the study period. Any deviation outside this alcohol intake restriction will be assessed on a case-by-case basis at Investigator's discretion (provided the subject's alcohol intake will not impact in the safety aspects and objectives of the study and the subject has a negative alcohol screen prior to dosing).

10.5.3.4 Caffeine

Aside from the caffeine administered as a NIMP in Part A, food or drink containing caffeine (including coffee, tea, cola, energy drinks or chocolates) will be avoided completely for a period of no less than 5 days prior to the first dose of NIMP/IMP and throughout the study period.

10.5.3.5 Poppy and Sesame Seeds

Subjects will be advised that they must not eat food containing poppy and / or sesame seeds for 3 days before each visit to the Clinical Unit, as consumption of poppy and / or sesame seeds can lead to a positive opiate result in the DOA test.

10.5.4 Other Life-Style Restrictions

10.5.4.1 Strenuous Exercise

Strenuous exercise must be avoided completely from 3 days before the first dose of NIMP/IMP until the final study visit.

10.5.4.2 Blood Donation

Subjects will be advised that they should not donate blood for at least 3 months after the final study visit or early termination.

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10.6 Investigational Medicinal Product

10.6.1 Identity

The identity of each IMP is detailed in Table 10.6.1.

Table 10.6.1 Identity of Investigational Medicinal Products

Treatment	Product Name	Strength	Presentation/Form	Route
Test IMP	ABX464	50 mg	Capsule	Oral
NIMP/Probe drugs	Caffeine	50 mg	Tablet	Oral
	Fluvoxamine	50 & 100 mg	Tablet	Oral

10.6.2 Receipt and Storage

ABX464 will be supplied by ABIVAX S.A.

The Sponsor must notify the Principal Investigator, or the Project Manager, prior to dispatch of the IMP supplies, and of the anticipated date of their arrival. IMPs should arrive at the study site at least 7 days before the first dosing day. The Sponsor shall address all supplies to:

The Production Manager

The Pharmacy
Simbec-Orion
Merthyr Tydfil Industrial Park
Merthyr Tydfil
CF48 4DR

Simbec-Orion will source the NIMPs from its approved supplier.

Upon receipt, supplies will be dealt with as per Simbec-Orion SOP SR-IMP 053. Temperature monitors included with shipments will be downloaded.

The IMP will be stored under quarantine in a segregated, study-specific area, not above 30 ºC in a secure, temperature-controlled pharmacy. The shipping documentation and Qualified Person (QP) certification will be reviewed. The supplies will subsequently be removed from quarantine and approved for issue to clinic.

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10.6.3 Assembly and Release

Subject specific packs of IMP will be provided by ABIVAX S.A., with a QP certificate.

10.6.4 Administration

In Part A, each subject will receive the following IMPs & NIMPs:

- **Test IMP:** a single dose of ABX464 50 mg oral capsule will be administered once daily on Days 4 to 17.
- **NIMP:** a single dose of caffeine 50 mg oral tablet will be administered on Day 1, 4 and 17.

In Part B, each subject will receive the following IMPs & NIMPs:

- **Test IMP:** a single dose of ABX464 50 mg oral capsule will be administered on 2 separate occasions on Days 1 and 11.
- **NIMP:** a single dose of fluvoxamine 100 mg oral tablet will be administered once daily on Days 2 to 11. This will be followed by a fluvoxamine tapering period of 50 mg for 7 days and then 25 mg for 7 days.

The IMP and NIMP will be administered within 30 mins of a standardised breakfast with 240 mL water. Subjects must remain seating upright for at least 4 h after every administration of caffeine (Part A) i.e. Day 1, 4 & 17.

IMP administration will be documented in the electronic CRF (eCRF).

10.6.5 Return/Destruction

All used IMP containers and unused IMP will be held under quarantine pending return/destruction.

The Sponsor must provide approval for return/destruction of all remaining IMP within 8 weeks study completion. After this period, a charge for storage will be incurred.

All returns will be arranged at the earliest available delivery date. For IMP destruction, the sponsor will receive the Certificate of Destruction 4 to 6 weeks from the date of removal from site.

10.6.6 Method of Assigning Subjects to Treatment Groups

This is an open-blind, non-randomised study; therefore, each subject will receive the same product in the same sequence.

Subjects will be numbered sequentially from 001 (*i.e.*, 001, 002 etc.). Replacement subjects will be assigned the same number as the subject they are replacing, however, 100 will be added to the number (*i.e.*, 101 would replace 001 etc.).

10.6.7 Selection of Doses in the Study

Part A

The dose of caffeine selected for this study is 50 mg. The dose level was selected to allow adequate detection of caffeine (and its metabolite paraxanthine) in plasma samples for PK analysis.

The dose of ABX464 selected for Part A of this study is 50 mg as this is anticipated as the recommended clinical dose during subsequent clinical trials. Multiple dosing for 14 days is considered an appropriate duration of dosing to obtain maximum induction of CYP isoforms.

Part B

The dose of ABX464 selected for Part B of this study is 50 mg. The dose level was selected to allow adequate detection of ABX464 (and its metabolite ABX464-N-Glu) in plasma samples for PK analysis, and this is anticipated as the recommended clinical dose during subsequent clinical trials.

The dose of fluvoxamine selected for this study is 100 mg once daily as this is the recommended clinical dose in the SmPC, and steady state plasma levels should be achieved following 10 days of once-daily dosing, which is considered an appropriate to obtain maximum inhibition of CYP1A2. To mitigate against the risk of withdrawal symptoms, following completion of 10 days of once daily fluvoxamine, subjects will complete a tapering period consisting of 50 mg once daily for 7 days, followed by 25 mg once daily for 7 days.

10.6.8 Selection and Timing of Dose for Each Subject

Doses will be administered between approximately 08:30 and 10:30 a.m. within 30 min of consumption of a standard breakfast. The composition of the breakfast and total proportion consumed will be noted in the study meal log. An example standard breakfast includes 120 grammes (g) of bread, 30 g of jam, 16 g of butter, 10 g of sugar, 240 mL of decaffeinated coffee or tea.

10.6.9 Blinding

The study is open-label.

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10.6.10 Prior and Concomitant Therapy

Prior Medication: Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken within 28 days (or 5 half-lives (whichever is longer) prior to the first dose of IMP. Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken during the 28 days before the first dose of IMP, with the exception of paracetamol (which may be taken as an analgesic to a maximum of 2 g in 24 h [500 mg 4 times a day]).

Inclusion of subjects who have taken prior medication will be reviewed on a case-by-case basis in relation to the safety aspects and objectives of this study.

Concomitant Medication: Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken throughout the duration of the study, with the exception of paracetamol (which may be taken as an analgesic to a maximum of 2 g in 24 h [500 mg 4 times a day]).

If intake of ***ANY*** prior or concomitant medication is necessary during the study, the daily dosage, duration and reasons for administration will be recorded on the subject's eCRF.

10.6.11 Treatment Compliance

Each dose of IMP and NIMP will be taken under supervision and a hand and mouth check conducted. The exact dosing time for each subject will be recorded on the subject's eCRF.

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10.7 Efficacy and Safety Variables

10.7.1 Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study assessments is provided in Table 10.7.1 and Table 10.7.2.

Simbec-Orion personnel who have been appropriately trained will carry out study procedures.

Where more than 1 procedure is scheduled for the same time-point, the following order of priority will apply:

1. PK blood sampling. Blood samples collected outside of the defined deviation windows will be recorded as protocol deviations: ± 1 min for samples collected up to 45 mins time-point (inclusive) and ± 5 mins for samples collected > 45 mins time-point.
2. Vital signs and 12-lead ECG (a window of ± 10 mins in relation to the nominal time-point is allowed).

All baseline assessments may be performed within the 1 h before dosing.

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Table 10.7.1 Study Flow Chart – Part A

Visits	Screening	Treatment Period[1]									Post-Study Follow-Up[2]
Days	**Days -28 to -2**	**Day -1**	**Day 1**	**Days 2-3**	**Day 4**	**Days 5-6**	**Days 7-15**	**Day 16[13]**	**Day 17**	**Days 18-19**	**10-14 days from Day 17**
Inpatient visit		X	X	X	X	X		X	X	X	
Outpatient visit							X				X
Informed Consent	X										
Inclusion/Exclusion[3]	X	X	X					X	X		
Demographics	X										
Height / Weight / BMI	X										X (weight only)
Medical History & Concurrent Conditions[3]	X	X	X								
Virology Tests	X										
COVID-19 Reverse Transcription Polymerase Chain Reaction (RT-PCR) Test		X									
Urine Drugs of Abuse (DOA) (including Alcohol and Cotinine)[3]	X	X						X			
Pregnancy[3, 4]	X(serum)	X(urine)						X(urine)			X(serum)
FSH[5]	X										
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X	X		X[6]		X[6]	X[6]	X[6]		X[6]	X[6]
Haematology	X	X		X[6]		X[6]	X[6]	X[6]		X[6]	X[6]
Coagulation	X	X		X[6]		X[6]	X[6]	X[6]		X[6]	X[6]
Urinalysis	X	X		X[6]		X[6]	X[6]	X[6]		X[6]	X[6]
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X				X[8]				X[8]	X
12-Lead ECG	X	X	X[9]		X[9]				X[9]	X[9]	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
IMP (ABX464) administration[10]					X	X	X	X	X		
NIMP (Caffeine) administration[11]			X		X				X		
PK Blood Sampling[12]			X	X	X	X			X	X	

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Part A Study Flow Chart Footnotes:

[1] The treatment period will be approximately 20 days duration, from the morning before dosing (Day -1) until 48 h post-Day 17 caffeine/ABX464 dose (Day 19). Subjects will arrive at the Clinical Unit on Day -1 and will be discharged 48 h post-Day 4 caffeine dose (Day 6). Subjects will return to the Clinical Unit each morning for daily administration of ABX464 (Days 7-16), and then will return to the Clinical Unit on the afternoon of Day 16. Subjects will remain in the Clinical Unit until 48 h post-Day 17 caffeine/ABX464 dose (Day 19).

[2] Post-study follow-up will be performed 10 to 14 days after receiving the last dose of IMP/NIMP on Day 17.

[3] Eligibility will be confirmed on Day -1 / prior to dose administration on Day 1. Continued eligibility will be confirmed on Day 16 / prior to dose administration on Day 17.

[4] For all female subjects at screening, then WOCBP on Days -1, 16 and at follow-up.

[5] For female subjects of postmenopausal status confirmed by serum FSH falling within the respective pathology reference range.

[6] Blood samples for biochemistry, haematology and coagulation parameters and urine samples for urinalysis parameters will be collected on Days 3, 6, 9, 12, 16, 19 and at the post-study follow-up visit only.

[7] Vital signs will be taken at pre-dose, 1, 2, 4, 8 h (on Days 1, 4 and 17), 24 and 48 h (on Days 2, 3, 5, 6, 18 and 19) and pre dose only on Days 7-15 and 16.

[8] Physical examinations will be completed at discharge on Days 6 and 19.

[9] ECGs: For Days 1, 4 and 17 - 3 to be done at the following timepoints: pre-dose, 2 h and 4 h. On Days 18 and 19, ECGs will be performed 24 and 48 h post-Day 17 dose.

[10] IMP (ABX464 50 mg) will be administered once daily on Days 4 to 17 within 30 mins of the consumption of a standardized breakfast with 240 mL water.

[11] NIMP (caffeine 50 mg) will be administered on Day 1, Day 4 and Day 17 with 240 mL water.

[12] PK blood samples (6 mL) will be collected for measurement of caffeine and its metabolite, paraxanthine at pre dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 18, 24, 36 and 48 h.

[13] On Day 16, participants will arrive at the Clinical Unit on the morning of Day 16 for ABX464 administration and blood sampling for biochemistry, haematology and coagulation parameters. Once these assessments are completed, participants will be discharged from the unit until readmission in the afternoon of Day 16. The remainder of the assessments for Day 16 will not be performed until admission to the Clinical Unit on the afternoon of Day 16.

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Table 10.7.2 Study Flow Chart – Part B

Visits	Screening	Treatment Period[1]								Post-Study Follow-Up[2]
Days	**Days -28 to -2**	**Day -1**	**Day 1**	**Days 2-9**	**Day 10[14]**	**Day 11**	**Day 12**	**Days 13-25**	**Day 26**	**3-5 days from Day 25**
Inpatient visit		X	X		X	X	X			
Outpatient visit				X				X[3]		X
Home dosing								X[4]		
Informed Consent	X									
Inclusion/Exclusion[5]	X	X	X		X	X				
Columbia-Suicide Severity Rating Scale [C-SSRS]	X	X		X[6]	X		X			X
Demographics	X									
Height / Weight / BMI	X									X (weight only)
Medical History & Concurrent Conditions[5]	X	X	X							
Virology Tests	X									
COVID-19 Reverse Transcription Polymerase Chain Reaction (RT-PCR) Test		X								
Urine Drugs of Abuse (DOA) (including Alcohol and Cotinine)[5]	X	X			X					
Pregnancy[5, 7]	X(serum)	X(urine)			X(urine)					X(serum)
FSH[8]	X									
Adverse Events	X	X	X	X	X	X	X	X		X
Biochemistry	X	X			X		X			X
Haematology	X	X			X		X			X
Coagulation	X	X			X		X			X
Urinalysis	X	X			X		X			X
Vital Signs	X	X	X[9]		X	X[9]	X[9]			X
Physical Examination	X						X			X
12-Lead ECG	X	X	X[9]			X[9]	X[9]			X
Concomitant Medication	X	X	X	X	X	X	X			X
IMP (ABX464) administration[10]			X			X				

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Visits	Screening	Treatment Period[1]								Post-Study Follow-Up[2]
Days	**Days -28 to -2**	**Day -1**	**Day 1**	**Days 2-9**	**Day 10[14]**	**Day 11**	**Day 12**	**Days 13-25**	**Day 26**	**3-5 days from Day 25**
NIMP (fluvoxamine) administration[11]				X	X	X	X	X		
PK Blood Sampling[12]			X			X				
Follow-up phone calls[13]								X	X	

Part B study Flow Chart Footnotes:

[1] The treatment period will be approximately 26 days duration (including a fluvoxamine tapering period), from the afternoon before dosing (Day -1) until 24 h post-Day 11 ABX464 dose (Day 12). Subjects will arrive at the Clinical Unit on Day -1 and will be discharged 24 h post-Day 1 ABX464 dose (Day 2). Subjects will return to the Clinical Unit each morning for daily administration of fluvoxamine (Days 3-10), and then will return to the Clinical Unit on the afternoon of Day 10. Subjects will remain in the Clinical Unit until 24 h post-Day 11 ABX464 dose (Day 12).

[2] Post-study follow-up will be performed 3 to 5 days after receiving the last dose of NIMP on Day 25.

[3] Subjects will be required to attend the Clinical Unit on Days 13, 14, 15 and 16 for the first five fluvoxamine tapering doses (Subject will be dosed at the Clinical Unit on Day 12 prior to discharge).

[4] Upon discharge from the Clinical Unit on Day 16, subjects will be provided the remainder of the required fluvoxamine tapering doses for at home dosing/self-administration on Days 17 to 25. Subjects are required to document each fluvoxamine dose administration in the paper participant dosing diary which the subject should return at the post-study follow-up visit.

[5] Eligibility will be confirmed on Day -1 / prior to dose administration on Day 1. Continued eligibility will be confirmed on Day 10 / prior to ABX464 dose administration on Day 11.

[6] On Days 2-9, C-SSRS will be completed on Day 6 only.

[7] For all female subjects at screening, then WOCBP on Days -1, 10 and at follow-up.

[8] For female subjects of postmenopausal status confirmed by serum FSH falling within the respective pathology reference range.

[9] Vital signs and ECGs will be performed pre-dose on Days 1, 11 and 12.

[10] IMP (ABX464 50 mg) will be administered on Days 1 and Day 11 within 30 mins of the consumption of a standardized breakfast with 240 mL water.

[11] NIMP (fluvoxamine 100 mg) will be administered once daily on Days 2 to 11 with 240 mL water, followed by a tapering period to mitigate against withdrawal symptoms consisting of 50 mg once daily for 7 days, followed by 25 mg once daily for 7 days.

[12] PK blood samples (6 mL) will be collected for measurement of ABX464 and ABX464-N-Glu at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10 and 12 h.

[13] Follow-up phone calls to check fluvoxamine withdrawal symptoms: Days 17, 20, 23 and 26.

[14] On Day 10, participants will arrive at the Clinical Unit on the morning of Day 10 for fluvoxamine administration and blood sampling for biochemistry, haematology and coagulation parameters. Once these assessments are completed, participants will be discharged from the unit until readmission in the afternoon of Day 10. The remainder of the assessments for Day 10 will not be performed until admission to the Clinical Unit on the afternoon of Day 10.

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10.7.1.1 Demographic and Background Assessments

The following demographic and background assessments will be performed during the study at the time-points specified in Table 10.7.1 and Table 10.7.2.

10.7.1.1.1 Demographics

Demographic data: age, year of birth, gender, height, weight and BMI.

Height in metres (to the nearest centimetre (cm)) and weight in kilogrammes (kg) (to the nearest 0.1 kg) in indoor clothing and without shoes will be measured. BMI = body weight (kg) / [height (m)]^2 will be calculated.

10.7.1.1.2 Medical History and Concurrent Conditions

Relevant medical history and current conditions will be recorded in the eCRF.

10.7.1.1.3 Virology Tests

Virology tests: HBsAg, HCV Ab, HIV test (antibodies to HIV-1 and HIV-2).

Virology tests will be analysed from the same serum sample for biochemistry analyses at Screening by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

10.7.1.1.4 Drugs of Abuse and Alcohol

Urine DOA screen (including alcohol and cotinine): Alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids/tetrahydrocannabinoids (THC), cocaine, cotinine, methadone, and opiates.

A **mid-stream** urine sample will be collected into a universal collection/storage container. At protocol-defined time-points when both urinalysis and drugs of abuse / alcohol screening are required, all urine analyses will be performed from a single approximately 30 mL urine sample.

Urine samples for DOA (including alcohol and cotinine) will be analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/manual kit(s)/method(s) of analyses. Assessments of urine sample quality (i.e., urine sample verification/adulteration) will be performed by measuring urine creatinine for urine DOA.

10.7.1.1.5 COVID-19 RT-PCR Testing

A nasopharyngeal and/or oropharyngeal swab will be collected during the study at the time-points specified in Table 10.7.1 and Table 10.7.2. A real-time reverse transcription polymerase chain reaction (RT-PCR) test will be performed by Simbec-Orion Laboratories, using the Menarini VitaPCR analyser.

10.7.1.1.6 Pregnancy Test, Menstrual and Obstetric History

Pregnancy tests will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory. Serum pregnancy tests will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser. Urine

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pregnancy tests will be performed manually using an appropriate pregnancy test kit/method(s) of analysis.

Serum FSH will be analysed from the same serum sample for biochemistry analyses at Screening for postmenopausal females only. **Serum** FSH analysis will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analysis.

10.7.1.2 Compliance with Inclusion/Exclusion Criteria

An Investigator will assess all participants against the study inclusion and exclusion criteria at Screening. Compliance will be re-confirmed on Day -1 / prior to dose administration on Day 1. Continued eligibility will be confirmed on Day 16 / prior to dose administration on Day 17 in Part A and on Day 10 / prior to dose administration on Day 11 in Part B.

10.7.1.3 Efficacy Assessments

Not applicable.

10.7.1.4 Safety Assessments

The following safety assessments will be performed at the time-points specified in Table 10.7.1 and Table 10.7.2.

10.7.1.4.1 Adverse Events

AEs and SAEs that occurred during the study along with their severity and relationship to study drug will be reported.

Per ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting:

An AE is defined as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction:

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

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whereby a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Serious Adverse Events

"SAE", "serious adverse reaction" or "unexpected serious adverse reaction" is defined as any AE, adverse reaction or unexpected adverse reaction, respectively, that

a. results in death,

Note: Death is an outcome (of an AE, of progressive disease, etc.) and not an AE in itself.

b. is life-threatening,

A life-threatening event places the patient 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.

c. requires hospitalisation or prolongation of existing inpatients' hospitalisation,

"In-patient hospitalisation" means that the patient has been formally admitted to a hospital for medical reasons, for any length of time. It does not include presentation to or care within an emergency department.

Complications that occur during hospitalisations are AEs. If a complication prolongs hospitalisation, it is an SAE.

d. results in persistent or significant disability or incapacity, or

e. consists of a congenital anomaly or birth defect.

f. Is otherwise "medically significant" (*e.g.,* that it does not meet preceding criteria, but is considered serious because treatment/intervention would be required to prevent one of the preceding criteria)

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An unexpected adverse reaction or Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as:

An (suspected, unexpected, serious) adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. IB for an unapproved investigational product of SmPC for an authorised product).

AEs will be monitored throughout the study from the signature of participant informed consent through to the post-study follow-up visit. All AEs will be recorded, whether considered minor or serious, drug-related or not.

All abnormal laboratory findings considered to be clinically significant will be recorded as AEs.

Recording of Adverse Events

All of the following details will be recorded in the subject's CRF for each AE:

- Full description of AE including body site, description of sign and symptoms and where possible full diagnosis.

- Date and time of onset.
- Ongoing (Yes/No)
- End Date/Stop date and time.
- Dechallenge/Rechallenge information
- Severity of event to be assessed by an Investigator in accordance with the definitions below.
- SAE (Yes/No) and seriousness criteria (if applicable)
- Relationship to IMP to be assessed by an Investigator in accordance with the definitions below.
- Action taken (if any).
- Outcome and details of any further follow-up.

Grades of Adverse Event Severity

Severity of AEs will be assessed according to Common Terminology Criteria for AEs (CTC-AE Classification) Version 5.0.

SEVERITY OF THE AE	DEFINITION
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*. *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Definitions of Adverse Event Causality

The following definitions will be used by an Investigator to describe the relationship between an AE and the IMP.

The following are the only definitions which will be used to describe the relationship between AEs and the IMP. Only 1 relationship definition will be used for each AE.

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Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

All SAEs must be reported by the Investigator site within 24 h of knowledge of the event by submitting an SAE form via email, hotline or fax to IntuVigilance:

IntuVigilance Limited

Cardinal Point, Park Road,

Rickmansworth WD3 1RE

Hertfordshire, UK.

o Hotline phone: +44 800 689 4129

o Email Address: safety@intuvigilance.com

o Fax number: +44 800 915 6753

SAE(s) will be collected throughout the study from the signature of participant informed consent through to the post-study follow-up visit. SAEs occurring after the follow-up period should be reported to the Sponsor if the investigator becomes aware of them.

The SAE Form must be completed as fully as possible with information relevant to the SAE(s) being reported. If it is not possible to complete all sections of the SAE Form within 24 hours, transmission of the form must not be delayed, and the outstanding information should be sent on a follow-up SAE Form. Follow-up SAE forms should be completed and transmitted following the same procedure.

IntuVigilance will notify the Sponsor and Sponsor's Responsible Physician of the SAE via e mail within 1 business day of receipt of the SAE form from site.

Expectedness and further reportability assessments will be completed by IntuVigilance and the Sponsor. AEs which meet all of the following criteria

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- Serious.
- Unexpected (i.e. is not consistent with the applicable product information e.g., Investigator's brochure for an unapproved IMP or SmPC for an authorised product).
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product.

will be classified as SUSARs and should be reported to the REC/Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and to the regulatory authorities in accordance with applicable regulatory requirements for expedited reporting. It is IntuVigilance's responsibility to report SUSARs to the REC/IRB/IEC and regulatory authorities.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Monitoring of Subjects with Adverse Events

In the event of any abnormalities considered to be clinically significant by the investigating physician, subjects will be followed up with appropriate medical management until:

- It has resolved/returned to normal or baseline.
- The event has stabilised at a level acceptable to the Investigator and is not considered to be clinically significant.

Pregnancy

Pregnancies must be reported by the Investigator site within 24h of first knowledge by submitting a pregnancy notification form via email or fax to IntuVigilance following the same procedures described for SAEs reporting and should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications.

Once consent has been obtained, pregnancy outcomes must be collected for females who took the IMP and the female partners of any males who took the IMP on the pregnancy outcome form and should be sent to IntuVigilance within 24 hours of the time the information is known. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. Pregnancy in itself is not regarded as an AE.

If the pregnancy outcome meets the SAE definition also complete an SAE Form. It is important to monitor the outcome of any pregnancies of subjects in order to provide SAE data on congenital anomalies, birth defects or spontaneous abortion.

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10.7.1.4.2 Laboratory Safety Assessments

Laboratory Safety Screen

Laboratory safety screen samples will be analysed by Simbec-Orion Laboratory Services. Printed laboratory test result reports will include normal reference ranges. A decision regarding whether the laboratory test result outside the normal reference range is of clinical significance or not shall be made by an Investigator/designee and the report will be annotated accordingly. Clinically significant laboratory test result abnormalities will be recorded on the AE page. Where deemed serious, these will be forwarded to IntuVigilance by the Investigator site on an SAE form. The normal reference ranges for laboratory test parameters will be detailed in the SLPDoc0024 Normal Reference Ranges and Alert Reference Values document.

Biochemistry Tests: ALT, ALP, AST, bicarbonate (HCO_3), total bilirubin, calcium (Ca), chloride (Cl), c-reactive protein (CRP), creatine kinase (CK), creatinine, glucose (fasting or random), gamma glutamyl transferase (GGT), potassium (K), total protein, sodium (Na), and urea.

Blood samples for biochemistry analyses for each time-point will be collected into an appropriately sized serum collection tube with or without a separator, and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses. Assessments of blood sample quality (*i.e.*, for sample verification) will be performed by measuring 3 indices [namely, Lipaemic (for Lipaemia), Haemolytic (for Haemolysis) and Icteric (for Icterus)] in serum.

Haematology Tests: Haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelet count, red blood cell count (RBC), red blood cell distribution width (RDW), white blood cell count (WBC), and WBC differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) (reported in absolute and percentage values).

Blood samples for haematology analyses for each time-point will be collected into an appropriately sized blood collection tube containing ethylenediaminetetraacetic acid (EDTA) and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

Coagulation Tests: Activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalised ratio (INR).

Blood samples for coagulation analyses for each time-point will be collected into an appropriately sized plasma collection tube containing buffered trisodium citrate solution (0.105 molarity (M) or 0.109 M, equivalent to 3.2% trisodium citrate) and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

Urinalysis Tests: Bilirubin, blood, glucose, ketones [or ketone bodies], leucocytes, nitrite, pH, protein, specific gravity (SG), and urobilinogen.

A mid-stream urine sample for each time-point will be collected into a 30 mL collection/storage container. Urinalysis will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory using an appropriate analyser/manual kit(s)/method(s) of analyses.

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In the event that the urinalysis 'dipstick' test result is positive for nitrite and/or 2+ or more reported for protein, blood, and/or leucocytes, then urine microscopy will be performed by reflex. The following test parameters will be reported: bacteria, casts (non-pathogenic), casts (pathogenic), crystals, epithelial cells, red blood cells and white blood cells. The urine microscopy will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

10.7.1.4.3 Other Safety Assessments

Vital Signs: Systolic/diastolic blood pressure and pulse rate.

Measurements will be recorded in the supine position after 10min supine. Blood pressure and pulse will be measured by the DINAMAP* Compact Vital Signs Monitor (Model TS) or equivalent. Normal ranges for vital signs are presented in APPENDIX 1.

Physical Examination

A physical examination will be performed by an Investigator. The examination will include ear/nose/throat, ophthalmological, dermatological, cardiovascular, respiratory, gastrointestinal, central nervous system (CNS), lymph nodes and musculoskeletal). An Investigator can examine other body systems if required, at their discretion.

ECG: Heart rate, PR interval, RR interval, QRS width, QT interval, and QTcF.

12-lead ECG recordings will be made using a Mortara ELI280 or equivalent. Each ECG trace should be labelled with the study number, subject screening/subject number (as applicable), subject year of birth. An Investigator will provide an interpretation of each tracing. Clinically significant abnormalities will be recorded on the AE page. Normal ranges for 12-lead ECG parameters are presented in APPENDIX 1.

Concomitant Medication

All prior and concomitant medications taken during the study will be recorded in the subject's eCRF (see Section 10.6.10).

Columbia-Suicide Severity Rating Scale (C-SSRS) (Part B only)

Suicide-related thoughts and behaviours will be assessed using the C-SSRS at screening and on study days as detailed in Table 10.7.2.

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10.7.2 Appropriateness of Measurements

All measurements performed in the study are standard measurements.

The total volume of blood to be collected from each subject during the study is documented in Table 10.7.3 and Table 10.7.4 is considered acceptable.

Table 10.7.3 Part A: Summary of Blood Volume

Procedure	Visit	No. of Samples	Blood Volume Per Sample (mL)	No. Treatment Periods	Blood Volume (mL)
Biochemistry	Screening[1]	1	4.5	N/A	4.5
	Day -1	1	4.5	N/A	4.5
	Day 3	1	4.5	N/A	4.5
	Day 6	1	4.5	N/A	4.5
	Day 9	1	4.5	N/A	4.5
	Day 12	1	4.5	N/A	4.5
	Day 16	1	4.5	N/A	4.5
	Day 19	1	4.5	N/A	4.5
	Post study[2]	1	4.5	N/A	4.5
Haematology	Screening	1	3.0	N/A	3.0
	Day -1	1	3.0	N/A	3.0
	Day 3	1	3.0	N/A	3.0
	Day 6	1	3.0	N/A	3.0
	Day 9	1	3.0	N/A	3.0
	Day 12	1	3.0	N/A	3.0
	Day 16	1	3.0	N/A	3.0
	Day 19	1	3.0	N/A	3.0
	Post study	1	3.0	N/A	3.0
Coagulation	Screening	1	2.7	N/A	2.7
	Day -1	1	2.7	N/A	2.7
	Day 3	1	2.7	N/A	2.7
	Day 6	1	2.7	N/A	2.7
	Day 9	1	2.7	N/A	2.7
	Day 12	1	2.7	N/A	2.7

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	Day 16	1	2.7	N/A	2.7
	Day 19	1	2.7	N/A	2.7
	Post study	1	2.7	N/A	2.7
PK Drug Concentration Measurement	Study period	15	6.0	3	270.0
				Total Blood Volume[3]	361.80

[1] From the biochemistry blood sample collected at the Screening visit, the serum pregnancy test (for female subjects only) and virology screen will be analysed from the same serum sample.
[2] From the biochemistry blood sample collected at the post-study follow-up visit, the serum pregnancy test (for female subjects only) will be analysed from the same serum sample.
[3] Please note: This total blood volume does not include any additional blood sample collection(s) for retest, unscheduled testing or additional tests required at the discretion of the Investigator/designee.
The exact volumes of each sample may change but the total volume of blood drawn for any subject will not exceed 450 mL.

Table 10.7.4 Part B: Summary of Blood Volume

Procedure	Visit	No. of Samples	Blood Volume Per Sample (mL)	No. Treatment Periods	Blood Volume (mL)
Biochemistry	Screening[1]	1	4.5	N/A	4.5
	Day -1	1	4.5	N/A	4.5
	Day 10	1	4.5	N/A	4.5
	Day 12	1	4.5	N/A	4.5
	Post study[2]	1	4.5	N/A	4.5
Haematology	Screening	1	3.0	N/A	3.0
	Day -1	1	3.0	N/A	3.0
	Day 10	1	3.0	N/A	3.0
	Day 12	1	3.0	N/A	3.0
	Post study	1	3.0	N/A	3.0
Coagulation	Screening	1	2.7	N/A	2.7
	Day -1	1	2.7	N/A	2.7
	Day 10	1	2.7	N/A	2.7
	Day 12	1	2.7	N/A	2.7
	Post study	1	2.7	N/A	2.7
PK Drug Concentration Measurement	Study period	15	6.0	2	180.0

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Total Blood Volume[3]	231.0

[1] From the biochemistry blood sample collected at the Screening visit, the serum pregnancy test (for female subjects only) and virology screen will be analysed from the same serum sample.
[2] From the biochemistry blood sample collected at the post-study follow-up visit, the serum pregnancy test (for female subjects only) will be analysed from the same serum sample.
[3] Please note: This total blood volume does not include any additional blood sample collection(s) for retest, unscheduled testing or additional tests required at the discretion of the Investigator/designee. The exact volumes of each sample may change but the total volume of blood drawn for any subject will not exceed 450 mL.

10.7.3 Primary Efficacy Variable(s)

Not applicable.

10.7.4 Drug Concentration Measurements

Plasma samples for drug and metabolite concentration measurements will be analysed at Charles River, using a validated liquid chromatography tandem mass spectrometry (LC MS/MS) method, according to applicable local SOPs.

10.7.4.1 Pharmacokinetic Blood Sampling

Blood samples (6 mL) for determination of plasma ABX464 / N-Glu and Caffeine / Paraxanthine levels will be taken into 6 mL Lithium Heparin tubes at the times specified in Table 10.7.1 and Table 10.7.2.

Immediately after sample collection, each sample collection tube will be identified with a barcoded label bearing details of the study number, subject number, sampling time-point, sample type (*i.e.*, sample matrix, *e.g.*, blood, etc), and a unique 9-digit sample identification number. The collected sample will then be processed by centrifugation at 1500 g at +4 degrees Celsius (°C) for 10 min.

Two (2) aliquots of plasma will be divided equally and transferred to two aliquot/storage tubes (Part A: 2 aliquots for Caffeine / Paraxanthine & Part B: 2 aliquots for ABX-464 / N-Glu), each labelled similarly to the original blood sample (bearing the same details of the study number, subject number, sampling time-point, and unique 9-digit sample identification number, except for the sample type [*i.e.,* sample matrix, *e.g.*, plasma etc]), and stored at the appropriate temperature as detailed in the sample handling manual. The date and time at which each PK sample are collected, received in the separating room, and subsequently placed in the appropriate freezer(s) will be recorded in the study documentation.

Full details of sample handling and processing can be found in the sample handling manual.

A repeat of an already collected PK sample is not permitted during the study.

10.7.4.2 Pharmacokinetic Urine Collection

Not applicable.

10.7.5 Pharmacodynamic Assessments

Not applicable.

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10.7.6 Other Assessments

Not applicable.

10.8 Data Quality Assurance

At the time the study is initiated, a representative of the Sponsor will thoroughly review the final protocol and eCRFs with the Principal Investigator and site staff. During the course of the study the Monitor will visit the Clinical Unit regularly to check the completeness of the subject's records (including the volunteer (subject) master files, laboratory and 12-lead ECG print-outs), the accuracy of entries into the eCRFs, the adherence to the final protocol and to ICH GCP E6 (R2) guidelines[1], the progress of enrolment and also to ensure the storage, handling and accountability of the IMP. The Principal Investigator and key study personnel will be available to assist the Monitor during these visits.

The Principal Investigator will give the Monitor, Auditor(s), the REC, and the MHRA direct access to relevant clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave Simbec-Orion. The Sponsor will maintain the confidentiality of all subject records, in line with Section 6.10 of the ICH GCP E6 (R2) guidelines[1] and the General Data Protection Regulation (GDPR)[5].

Study data will be fully documented in the eCRFs and study logbooks. Dated signatures will be given to account for all interventions in the study by research staff.

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

For the purposes of this study the source data will be recorded as detailed in Table 10.8.1:

Table 10.8.1 Summary of Source Documentation Location

Data	Source Documentation			
	Volunteer Master File	eCRF[1]	Paper Source File/Workbook	Other
Evidence of healthy subject status/primary disease condition for entry into clinical study	X			
Demographic data		X		
Medical history and age	X			
Inclusion and exclusion criteria		X		
Informed consents[2]	X	X		
Subject participation in the clinical study		X		
Screening number				X (screening log)
Subject number		X	X	X (enrolment log)
AEs		X		
SAEs				X (SAE form)
Pregnancies				X (Pregnancy notification and outcome form)
Previous and on-going therapy	X			
Concomitant medication		X		

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Results of study examinations (e.g., 12-lead ECGs, vital signs and laboratory safety tests)[3]		X	X	
Physical Examination[4]		X		
Study visit dates		X		
Administration of IMP and NIMP		X		
Blood PK sample collection times		X		
Blood safety sample collection times		X		
C-SSRS questionnaires			X	
Participant dosing diary			X	

[1] In the event staff are unable to enter data directly into the eCRF (e.g. technical/internet issues), data will be entered directly into a back-up paper source workbook at the time of assessment, then transcribed and subsequently QC'd.
[2] The original ICFs will be maintained in the Study Officer file during the clinical phase and will then be transferred to the Project Manager for archiving with the Investigator Site File (ISF)at the end of the study.
[3] The 12-lead ECG trace and laboratory safety test print-out will be stored in the paper source workbook.
[4] In the eCRF, the date and time of each physical examination will be recorded. Any abnormal findings will be captured on the Medical History form at Screening and as an Adverse Event during clinical conduct.

The above table indicates where source data will be recorded but for completeness the following information will also be recorded in the volunteer master file:

- Clinical study code.
- Study visit dates (pre-dose; post-dose).
- IMP administration (date of last dose).
- Results of any key safety and efficacy measures from the clinical study that in the opinion of an Investigator should be noted.
- Any concomitant medications used to treat the subject during the study that in the opinion of an Investigator should be noted.

The data collected in the eCRFs during the study will be subject to quality control checking by clinical staff prior to sign off.

Designated investigator site staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements. Staff will not be given access to the eCRF until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Biometrics group. The Investigator must certify that the data entered into the e-CRF are complete and accurate.

The study will be subject to an independent audit by the Simbec-Orion Quality Assurance (QA) Unit as outlined in Simbec-Orion SOP GRP-QA 002.

Independent clinical quality assurance audits may be performed at any time during or following completion of the study by the Sponsor, or its authorised agents, and Regulatory Authorities and/or the REC.

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10.9 Statistical Methods and Determination of Sample Size

10.9.1 Statistical and Analytical Plan

A statistical analysis plan (SAP) will be written by Simbec-Orion and agreed by ABIVAX S.A. prior to the locking of the database and subsequent reporting of the study data.

10.9.1.1 Study Variables/Endpoints

10.9.1.2 Analysis Sets

Safety Set: All enrolled subjects who receive at least 1 dose of IMP/NIMP will be included in the safety analysis.

PK Set: Subjects will be included in the PK Set where they have received all doses of IMP/NIMP up to and including Day 17 for Part A and Day 11 for Part B and comply with the following criteria:

- Do not have an occurrence of vomiting (that occurs at or before 2 times median time to maximum observation concentration (C_{max}; T_{max}) of the appropriate treatment) or diarrhoea which renders the concentration profile unreliable;
- Do not use a concomitant medication which renders the concentration profile unreliable;
- Do not have a pre-dose concentration that is greater than 5% of the corresponding C_{max};
- Have at least one PK sample with concentration above the lower limit of quantitation (LLOQ);
- Do not violate the protocol in such a way that may invalidate or bias the results (major protocol violators).

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10.9.1.3 Description of Statistical Methods

All statistical analysis will be performed using statistical analysis software by SAS Institute Inc., USA (SAS®) (the most up to date version will be used and this will be documented in the SAP).

10.9.1.3.1 Demographic and Background Data

All demographic and background data will be listed, in addition:

Disposition: Subject disposition will be listed with any withdrawals flagged. Frequencies (number and %) of the total number of subjects dosed, completed and prematurely discontinued (including reason for discontinuation) from the study will be summarised. Additionally, the frequency of subjects within each analysis set will be summarised.

Demographics: Demographic data will be listed. Descriptive statistics (number of subjects in the analysis population (N), number of subjects with non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum) will be tabulated for the continuous variables age, height, weight and BMI and frequencies (number and %) for the categorical variable gender.

10.9.1.3.2 Efficacy Data

Not applicable.

10.9.1.3.3 Safety Data

The safety endpoints are:

- AEs.
- Laboratory safety (biochemistry, haematology, coagulation and urinalysis).
- Vital signs (systolic/diastolic blood pressure, pulse rate).
- 12-lead ECG (heart rate, RR interval, PR interval, QRS duration, QT interval and QTcF interval).

All safety data will be listed, in addition:

AEs: All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (the most up to date version that is available at the time of database build will be used and will be listed in the Data Management Plan (DMP)). The MedDRA dictionary will not be updated during the course of the study.

All AEs, including those which occurred prior to the first dose of IMP/NIMP, will be listed. Only treatment emergent adverse events (TEAEs), i.e., existing conditions that worsen or events that occur during the course of the study after administration of IMP/NIMP, will be included within the summary tables.

An overall summary of AEs will be produced including the number of TEAEs; the number and % of subjects reporting at least 1 TEAE, serious TEAE, TEAE leading to withdrawal from the study; the number and % of subjects reporting TEAEs by severity and relationship to IMP/NIMP.

The number of TEAEs and the number and % of subjects reporting at least 1 TEAE will be tabulated by system organ class (SOC) and preferred term. A subject reporting multiple episodes of a particular AE within a treatment period will only contribute 1 count towards the corresponding SOC and preferred term.

In addition, the number and % of subjects reporting TEAEs will be tabulated by maximum severity and strongest relationship to IMP/NIMP. For the summary of TEAEs by severity, if a subject has multiple events occurring within the same SOC or preferred term the event with the highest severity will be counted. Similarly, for TEAEs by relationship to IMP/NIMP, if a subject has multiple events occurring within the same SOC or preferred term, the event with the highest association to IMP/NIMP will be counted.

Laboratory Safety: Biochemistry, haematology, coagulation and urinalysis parameters will be listed with any out of normal range values flagged. Laboratory test results which are out of normal range will also be presented separately along with normal reference ranges. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day -1) values at each time-point will be tabulated.

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Vital Signs: Vital signs parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day 1 pre-dose) values at each time-point will be tabulated.

12-Lead ECG: 12-Lead ECG parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day 1 pre-dose) values at each time-point will be tabulated.

10.9.1.3.4 Pharmacokinetic Data

Concentration-Time Data: Individual plasma caffeine/paraxanthine (Part A) and ABX464/ABX464-N-Glu (Part B) concentration-time data will be listed. Concentration-time data will also be summarised. The descriptive statistics presented will be N, n, arithmetic mean, geometric mean, SD, coefficient of variation (CV%), minimum, median and maximum. Individual and mean concentration-time data will also be plotted on both linear and semi-logarithmic scales.

For the purposes of summarizing and plotting concentration-time data, concentration value(s) below the LLOQ will be assigned a value of zero if the timepoint is prior to treatment and LLOQ/2 otherwise.

Derived PK Data: The following PK parameters will be derived from plasma caffeine/paraxanthine (Part A) and ABX464/ABX464-N-Glu (Part B) concentration-time data following administration of each NIMP/IMP using Phoenix WinNonlin (the most up to date version will be used and this will be documented in the SAP).

For the purposes of calculating PK parameters, concentration value(s) below the LLOQ will be assigned a value of zero.

C_{max}	maximum concentration.
T_{max}	the time to maximum observed concentration.
λ_z	elimination rate constant.
$t_{1/2}$	terminal elimination half-life.
AUC_{0-t}	area under the concentration-time curve (AUC) from the time of dosing to the time of the last measurable concentration.
AUC_{0-inf}	the AUC extrapolated to infinity.
$AUC_{\% extrapolated}$	residual area.
CL/F	Total apparent clearance following extravascular administration
Vz/F	Apparent volume or distribution following extravascular administration

Derived PK endpoints will be listed along with the points used to calculate elimination rate constant (λ_z) (lower, upper and number used) and R^2 adjusted. The derived PK endpoints will also be summarised. The descriptive statistics presented will be N, n, mean, SD, coefficient of

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variation (CV%), minimum, median, maximum and geometric mean (with the exception of T_{max}).

Statistical analysis of the derived pharmacokinetic parameters to help understand the DDI potential for ABX464 to inhibit, induce, or be a substrate for CYP1A2, will be performed using the PK Set. The primary pharmacokinetic endpoints of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} will be log-transformed and analysed using an analysis of variance (ANOVA) model including fixed effects for treatment and subject. Point estimates and 90% confidence intervals (CIs) will be constructed for the contrasts of:

Part A

- caffeine alone on Day 1 versus caffeine dosed simultaneously with ABX464 on Day 4
- caffeine alone on Day 1 versus caffeine dosed simultaneously with ABX464 on Day 17 following 14 days of daily dosing of ABX464

Part B

- ABX464 alone on Day 1 versus ABX464 dosed simultaneously with fluvoxamine on Day 11 following 10 days of daily dosing of fluvoxamine

These estimates will then be back-transformed to provide estimates of the ratios of the geometric LSMeans and corresponding 90% confidence intervals.

10.9.1.3.5 Other Data

Not applicable.

10.9.2 Sample Size Calculation

Based on data from a previous Single-Dose Two-Way Cross-Over Caffeine Study[6], the intra-subject CV% for $AUC_{0\text{-}inf}$ was approximately 24.2%. Using the method of Diletti[7], a sample size of 22 subjects is considered sufficient to detect a 20% treatment difference with a power of 80% and alpha of 5%, based upon a geometric mean ratio of 1. To allow for a higher CV%, dropouts or subjects who otherwise fail to complete the study, 24 subjects will be enrolled in Part A of the study.

From PK report ABX464-FE-001[8], the total CV% following a fed single dose was 46% for C_{max}, 42% for $AUC_{0\text{-}t}$ and 37% for $AUC_{0\text{-}inf}$. Based on a conservative estimate that the intra-subject CV% contributes 60% to total CV%, the intra-subject CV% for C_{max} is estimated at 27.6%. Rounding this to 30.0% to mitigate against an underpowered study and using the method of Diletti[7], a sample size of 32 subjects is considered sufficient to detect a 20% treatment difference with a power of 80% and alpha of 5%, based upon a geometric mean ratio of 1. To allow for a higher CV%, dropouts or subjects who otherwise fail to complete the study, 36 subjects will be enrolled in Part B of the study.

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11 PRACTICAL CONSIDERATIONS

11.1 Storage of Data

The Investigator site file (ISF) and associated study documentation will be archived for at least 25 years after the end of the study (last participant last visit) as per European Medicine Agency Guideline INS/GCP/856758/2018[9]. The study documentation may be transferred to an offsite storage facility during this period but will remain under the control of Simbec-Orion.

The Sponsor has delegated the set up and maintenance of the Sponsor trial master file (TMF) to Simbec-Orion. The TMF will be returned to the Sponsor at the end of the study, who will archive it as per regulation.

11.2 Protocol Amendments

Changes in the study protocol must take the form of written protocol amendments and shall require the approval of all persons responsible for the study (see Section 1).

A protocol amendment is deemed to constitute a substantial protocol amendment if it is considered to be likely to affect to a significant degree either:

a. the safety or physical or mental integrity of the subjects of the study.
b. the scientific value of the study.
c. the conduct or management of the study.
d. the quality or safety of any IMP used in the study.

Such amendments must be submitted to the REC responsible for the study and the MHRA for approval prior to implementation.

Protocol amendments required for urgent safety reasons may be implemented immediately. However, the REC and MHRA must be notified in writing within 3 days of the measures taken and the reasons for implementation.

All other amendments shall be deemed to be non-substantial and as such do not need the prior approval of the REC and the MHRA.

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11.3 Confidentiality

The confidentiality of the study must be maintained at all times and the Principal Investigator must not reveal any information relating to the study without express permission from the study Sponsor.

11.4 Study Report and Publication Policy

Simbec-Orion will investigate and analyse the data generated with all due speed.

A draft study report will be sent to the Sponsor for review. The Sponsor will forward any comments on the draft study report to the Project Manager within the agreed timelines. Upon receipt of these comments a final, QA approved report will be issued with all due speed. A copy of the report will be forwarded to the Sponsor.

The Principal Investigator will obtain the Sponsor's written permission before any information concerning this study is submitted for publication.

11.5 General Data Protection Regulation (GDPR)

ABIVAX S.A. as European sponsor assures to comply with the responsibilities set by the GCP (Directive 2005/28/EC of 8 April 2005 of the European Parliament and of the Council) and the European General Personal Data Protection Regulation 2016/679.

Simbec-Orion's Clinical Pharmacology Unit is a UK based Clinical Research Organisation and will be acting as the data controller. Simbec-Orion will hold volunteer data on our systems and the Volunteer Master File. The personal data that volunteers will provide for the study, will be processed exclusively upon its consent, which they can revoke at any time and without providing any justification. The possible withdrawal will be valid only for the future, without this however affecting the lawfulness of the treatment based on the consent given before the revocation. Volunteers consenting to the study are consenting to their data being processed in the UK, therefore the Data Protection Act 2018 is to be followed in addition to European General Personal Data Protection Regulation 2016/679.

Personal data of the volunteer shall be processed in a manner that ensures it has appropriate security. This includes protection against unauthorised or unlawful processing and against accidental loss, destruction or damage and by using appropriate technical or organisational measures. One such measure is by the Investigator ensuring that the volunteers' personally identifiable information should be replaced through the use of pseudonymisation.

On the eCRFs or other documents submitted to ABIVAX S.A./Simbec-Orion volunteers will NOT be identified by their names but by the assigned volunteer number (panel/screening/subject number) to ensure confidentiality of the volunteers' information and that data minimisation principles are maintained. If volunteer names are included in error on copies of documents submitted to ABIVAX S.A./Simbec-Orion volunteers', the names (except for initials) will be erased or securely destroyed and the assigned volunteer number added to the document.

This will be managed as a data breach and will be handled in accordance with Simbec-Orion's internal data breach policies and processes.

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12 REFERENCES

[1] European Medicine Agency (EMA). 2016. ICH (International Council on Harmonisation) Guideline for Good Clinical Practice (GCP) E6(R2) (CPMP/ICH/135/95). [online] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-goodclinical-practice-step-5_en.pdf [Accessed: 12 October 2020].

[2] Investigator's Brochure for ABX464 – Inflammatory Bowel Diseases (IBD). Current Version.

[3] Patient Information Leaflet (PIL) (or equivalent) for Caffeine.

[4] Summary of Product Characteristics (SmPC) for Fluvoxamine.

[5] EUR-Lex. 2016. Regulation (European Union (EU)) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). [online] Available from: https://eurlex.europa.eu/eli/reg/2016/679/oj [Accessed: 12 October 2020].

[6] Muhammad M Hammami and Syed N Alvi, Large Intra-Subject Variability in Pharmacokinetics: Randomized Cross-over Study of Single Caffeine Product. 2017. Drug Research 67(9)

[7] E. Diletti, D. Hauschke and V.W. Steinijans. Sample size determination for bioequivalence assessment by means of confidence intervals. International Journal of Clinical Pharmacology Therapy and Toxicology. 1991. Vol 29 No. 1 (1-8).

[8] PK Report ABX464-FE-001: An open, randomized study, to investigate the potential food effect on pharmacokinetic parameters of ABX464 administered orally to healthy male subjects. 2018. Version 1.0

[9] European Medicine Agency (EMA). 2018. Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) (INS/GCP/856758/2018) Good Clinical Practice Inspectors Working Group (GCP IWG). [online] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-contentmanagement-archiving-clinical-trial-master-file-paper/electronic_en.pdf [Accessed: 12 October 2020].

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APPENDIX 1: NORMAL RANGES FOR VITAL SIGNS AND ECG PARAMETERS

Vital Sign Parameters	
Pulse Rate	40-90 bpm
Systolic Blood pressure	90-140 mmHg
Diastolic Blood pressure	50-90 mmHg

ECG Parameters		
Heart Rate (HR)	40-90 bpm	
PR Interval	120-220 ms	
QRS Width	70-120 ms	
QT Interval	N/A	
QTc Interval - QTcF	Male: 350-450 ms	Female: 350-470 ms

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APPENDIX 2: DECLARATION OF HELSINKI (BRAZIL, 2013)

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for medical-research-involving-human-subjects/

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