CLINICAL STUDY PROTOCOL
ABX464-401 (MiR-AGE Study)

Sponsor:	ABIVAX 5, rue de la Baume 75008 Paris FRANCE
Investigational product:	ABX464
Product code:	ABX464
Therapeutic indication:	Adult patients infected by SARS-CoV-2 with high-risk of COVID-19 associated respiratory failure
Study code:	ABX464-401
EudraCT number:	2020-001673-75
Phase	2/3
Protocol title:	A phase 2/3, randomized, double blind, placebo-controlled study to evaluate the efficacy and the safety of ABX464 in treating inflammation and preventing COVID-19 associated acute respiratory failure in patients aged ≥ 65 and patients aged ≥18 with at least one additional risk factor who are infected with SARS-CoV-2. (the MiR-AGE study).
Document version number:	1.2 (DEU)
Release date:	11 May. 2020

CONFIDENTIALITY STATEMENT

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This information should not be disclosed to any third party without the prior written consent of ABIVAX

CLINICAL STUDY PROTOCOL VALIDATION PAGE

Study code	ABX464-401
EudraCT number	2020-001673-75
Detailed Title	A phase 2/3, randomized, double blind, placebo-controlled study to evaluate the efficacy and the safety of ABX464 in treating inflammation and preventing COVID-19 associated acute respiratory failure in patients aged ≥ 65 and patients aged ≥18 with at least one additional risk factor who are infected with SARS-CoV-2. (the MiR-AGE study).
Document date & version	11-May-2020 / Version 1.2 (DEU)
Validation	Prof. Hartmut J. Ehrlich, M.D. (CEO, CMO): Date:
	Paul GINESTE (VP, Clin Ops): Date:
	Alexandra Pearce (VP, Regulatory Affairs): Date:

CONTACTS

Sponsor	**ABIVAX** 5 rue de la Baume 75008 PARIS - France **Prof. Hartmut J. Ehrlich, M.D.** CEO, Chief Medical Officer Cell: +33 (0)6 15 16 20 19 **Dr Paul GINESTE** VP, Clinical Operations Cell: + 33 (0)6 25 83 07 83
Coordinating investigator (EU)	**Dr. Eric CUA** CHU de Nice - Hôpital Archet 1 CS 23079 151 route de St Antoine de Ginestière 06202 NICE cedex 3 FRANCE Tel. : +33 (0)4 92 03 54 67
Central Laboratory	**Hematology Department** Inserm UMR-S 1140 (Team 1) and Director of Biosurgical Research Lab (Carpentier Foundation) Paris Descartes University and European Georges Pompidou Hospital, Paris, France
miRNA-124 determination	**Acobiom** Cap Delta, 1682 Rue de la Valsière, 34790 Grabels – France
Quantitative analysis of SARS-CoV-2	**Hematology Department** Inserm UMR-S 1140 (Team 1) and Director of Biosurgical Research Lab (Carpentier Foundation) Paris Descartes University and European Georges Pompidou Hospital, Paris, France
Pharmacovigilance	**IntuVigilance Limited** Scotsbridge House, Scots Hill Rickmansworth WD3 3BB Hertfordshire – UK

INVESTIGATOR AGREEMENT PAGE

EudraCT number 2020-001673-75

Detailed Title: A phase 2/3, randomized, double blind, placebo-controlled study to evaluate the efficacy and the safety of ABX464 in treating inflammation and preventing COVID-19 associated acute respiratory failure in patients aged ≥ 65 and patients aged ≥18 with at least one additional risk factor who are infected with SARS-CoV-2. (the MiR-AGE study).

I have carefully read all the pages of this clinical study protocol and I agree to the following:

- To conduct the study as outlined in the protocol, any mutually agreed future protocol amendments and with all the terms and conditions set out by ABIVAX.
- Not to implement any changes in the procedures described in the protocol without the prior approval of the sponsor and prior to review and written approval by the Ethics Committee and/or Regulatory Authorities, unless instructed otherwise by the Regulatory Authorities or the wellbeing of patients is jeopardized.
- To conduct the study in accordance with the ICH GCP (R2) guidelines, US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations), the European Union Clinical Trials Directive 2005/28/EC, EudraLex GMP guidelines Annex 13, the provisions of the Helsinki Declaration, and relevant legislation in force.
- I am thoroughly aware of the study drug specifications and adverse events as described in the protocol and the current Investigator's Brochure and any other information provided by the Sponsor.
- To ensure that sub-investigator(s) and other relevant members of my staff involved in the study are fully aware of their responsibilities regarding this study and will conduct the study according to the protocol.

Investigator's Name: _____

Investigator's Signature: _____

Date: _____

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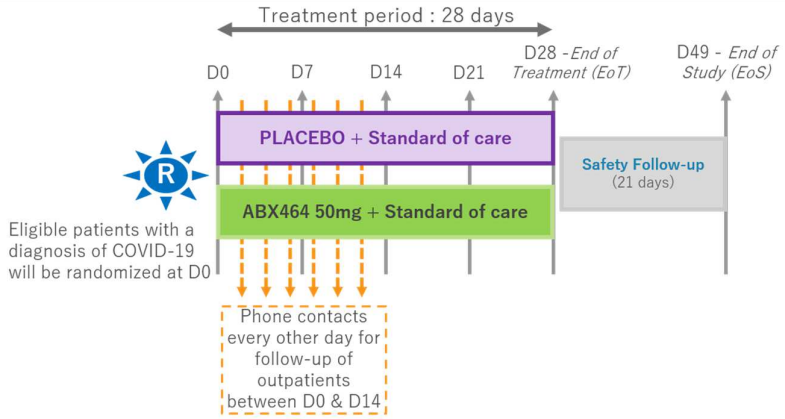
ABBREVIATIONS

Abbreviation or Term	Definition
ABX	**Abivax**
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvate transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
BMI	Body Mass Index
CBC	Cap Binding Complex
CI	Confidence Interval
Cmax	peak plasma concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
COVID-19	Corona Virus Disease provoked by SARS-CoV-2
CRF	Case Report Form
CRP	C-Reactive Protein
CTC-AE	Common Terminology Criteria for Adverse Events, version 5.0
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome
DBP	Diastolic Blood Pressure
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDTA	ethylenediaminetetraacetic acid
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GHAS	Global Histological Assessment Score
GLDH	Glutamate Dehydrogenase
GM	Geometric Mean
H	Hours
HIV	Human Immunodeficiency Virus
HR	heart rate
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-*X*	Interleukine *X*
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum
miR	micro-RNA
mL	Milliliter
mmHg	millimeters of mercury
NIV	Non-Invasive mechanical Ventilation
NOAEL	No Observed Adverse Effect Level
o.d.	Once Daily
PCSA	potentially clinically significant abnormalities
PD	pharmacodynamics
PK	pharmacokinetics
PT	Preferred Term
QoL	Quality of Life
QTc	heart-rate–corrected QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) using Bazett's formula
R	Accumulation ratio
RNA	Ribonucleic Acid
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
t1/2	terminal half-life
TB	Tuberculosis
TEAE	treatment emergent adverse event
tmax	time to peak plasma concentration
TMS	Total Mayo Score
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
ULN	Upper Limit Normal
Vd/F	volume of distribution
vs.	Versus
W	Week

SYNOPSIS

Study n°	ABX464-401	**Clinical Phase**	2/3
		Type of Study	Efficacy, Safety Study
Study title	A phase 2/3, randomized, double blind, placebo-controlled study to evaluate the efficacy and the safety of ABX464 in treating inflammation and preventing COVID-19 associated acute respiratory failure in patients aged ≥ 65 and patients aged ≥18 with at least one additional risk factor who are infected with SARS-CoV-2. (the MiR-AGE study).		
Short title	Phase 2/3 study of ABX464, once daily oral capsule, in high risk patients infected by SARS-CoV-2 prior to COVID-19 associated respiratory distress.		
Investigators and study centers	Approximately 50 sites (either hospital, or nursing home linked to hospital) located in Europe will participate in the study.		
Study Duration	Recruitment period: Jun. 2020 – Oct. 2020 (3 months) Overall Study period: Jun. 2020 – Jan. 2021 (7 months)		
Investigational product	Clinically, SARS-CoV-2 or COVID-19 infection can lead to a cytokine storm syndrome, acute respiratory distress syndrome (ARDS) and multiple organ failure. The hyperinflammatory syndrome associated with COVID-19 disease severity includes increased MCP1, IL-1b, TNFa, IL-17, G-CSF and IL-6 levels. ABX464 is a small molecule that binds the Cap Binding Complex (CBC), a protein complex sitting at the 5' ends of RNAs and that is involved in fueling cellular RNA integrity (e.g. splicing). ABX464 does not affect RNA biogenesis from cellular genes. ABX464 enhances the splicing of a long non-coding RNA to up-regulate microRNA miR-124, a well-known physiological inhibitor of systemic and pulmonary inflammation (potent reduction of MCP1, IL-1b, TNFa, IL-17, G-CSF and IL-6). ABX464 has anti-inflammatory properties in DSS and rheumatoid arthritis models, with good systemic and tissue bioavailability in blood, lung, kidney and brain. Administration of ABX464 has demonstrated clinical efficacy in patients with moderate to severe Ulcerative Colitis (UC). In addition, ABX464 has recently been tested in primary pulmonary cells infected by with SARS-CoV-2 (MucilAir cells). At 48h post infection, the viral load measured in the supernatant by qPCR was reduced by 1 log with ABX464 and even 2 logs with its active metabolite: ABX464-N-glucuronide. ABX464 was safe and well tolerated in more than 300 volunteers and patients in phase 1 and 2 clinical trials some of whom have been treated for over two years.		
Study Design and Methodology	This phase 2/3 study will evaluate the efficacy and safety of ABX464 50mg QD (oral capsule), on treating inflammation and preventing acute respiratory failure in patients infected with SARS-CoV-2. Eligible patients will be randomized according to a 2:1 ratio into 2 treatment cohorts as follows: - Standard of Care + Placebo cohort: 344 patients - Standard of Care + ABX464 50mg QD: 690 patients Upon randomization, patients will be stratified according to: - Age ≥ 65 years *or* < 65 years (with at least one risk factor) - Inpatient *or* outpatient, at the time of enrolment <u>Study design:</u> The study will consist of 2 periods: - Treatment phase: randomized patients will be treated for 28 days - Safety follow-up phase of 21 days after which the End of Study visit (EOS) will be performed.		

Study n°	ABX464-401	**Clinical Phase**	2/3
		Type of Study	Efficacy, Safety Study



From Day 0 onwards, randomized patients will be followed by the investigational site at 7 days (D7 +/- 2 days), 14 days (D14 +/- 2 days), 21 days (D21+/- 2 days) and finally 28 days (D28 +/- 2 days) after randomization. A long-term follow-up (3 months) looking at lung function is planned and will be part of an upcoming protocol amendment.

Should a patient be hospitalized at D0, Day 7 visit will be an on-site visit.

Should a patient not be hospitalized, considering a quarantine period might be applied for infected patients, a remote medical monitoring will be performed by the investigator or his designee every 2 days from D0 and until D14. Every attempt to perform the Day 7 on-site visit should be made anyway. For outpatients, an oximeter will be provided at Day 0. During the remote medical monitoring, the patient will be asked to self-measure every day the oxygen saturation, body temperature and will be asked for any potential signs of COVID-19 infection worsening. Subsequent, D14, D21 and D28 will be on-site visits.

If no quarantine period is applied or if patient migration to the study site is acceptable as per local regulation, outpatients will perform a D7 visit on-site, and the same examinations as hospitalized patients will be done.

At enrollment/randomization visit, all patients should be diagnosed for SARS-CoV-2 infection by PCR.

Approximately 1034 patients will participate in this study.

Study Objectives and endpoints

Primary Objective and endpoint:

The primary objective of the study is to determine the efficacy of ABX464 50mg to prevent respiratory failure or death in study patients.

- *Rate of patients who do not require use of high-flow oxygen (use of high-flow oxygen being defined as settings of 3 L/min or greater AND with at least one SpO2 measurement < 92%, with or without O2 supplementation) or non-invasive mechanical ventilation (IMV and NIV, respectively) within 28 days and who are alive at the end of the 28 days period.*

Secondary Objectives and endpoints:

The secondary objectives are:

To evaluate the proportion of patients requiring hospitalization during the study compared to the {Standard of care + placebo} group

- *Rate of patients hospitalized in both treatment groups*

To assess the proportion of patients reporting each severity rating on a 7-point ordinal scale during the course of the study compared to the {Standard of care + placebo} group

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		Type of Study	Efficacy, Safety Study

- *Percentage of patients reporting each severity rating on a 7-point ordinal scale at each study visit (i.e. Not hospitalized, no limitations on activities; Not hospitalized, limitation on activities; Hospitalized, not requiring supplemental oxygen; Hospitalized, requiring supplemental oxygen; Hospitalized, on non-invasive ventilation or high flow oxygen devices; Hospitalized, on invasive mechanical ventilation or ECMO; Death);*

To assess the time to an improvement of one category of the 7-point on an ordinal scale from baseline, compared to the {Standard of care + placebo} groups

- *Mean change in the ranking on an ordinal scale from baseline to days 7, 14, 21, and 28*

To evaluate and compare the effect of ABX464 on oxygen saturation before hospitalization

- *% change and AUC over time of oxygen saturation measured by daily pulse oximetry before hospitalization*

To evaluate and compare the effect of ABX464 on oxygen saturation level at the end of the study treatment

- *Rate of patients with SpO2 ≤94% and rate of patients with SpO2 ≤92% at Day 28*

To evaluate and compare the effect of ABX464 on immunophenotyping (in selected sites only) and cytokines levels during the study in hospitalized patients enrolled in both treatment groups.

- *Change from enrolment in inflammatory markers in plasma (i.e. MCP-1, MIP-1 α, G-CSF, IL-1b, IL-2, IL-6, IL-7, IL-10, IL-17, INFg and TNFa) and in immune phenotype and assessment of cell-activation markers in PBMCs at D14, D28 for hospitalized patients only.*

To evaluate the proportion of patient requiring oxygen supplementation (>3L/min) during the study compared to the {Standard of care + placebo} group.

- *Rate of patients requiring oxygen supplementation in both treatment groups.*

To assess the time to hospitalization (all causes and Covid-19 related hospitalization) during the study compared to {Standard of care + placebo} treated group.

- *Time to hospitalization (log rank) from baseline in both treatment groups.*

To evaluate the time to application of *invasive and non-invasive mechanical ventilation (IMV and NIV, respectively) or high flow oxygen therapy* excluding simple oxygen supplementation) and oxygen supplementation during the study compared to {Standard of care + placebo} treated group.

- *Time to assisted ventilation and oxygen supplementation (log rank) from baseline in both treatment groups.*

To assess the IMV and/or NIV duration compared to {Standard of care + placebo} treated group.

- *Number of days of assisted ventilation in both treatment groups.*

To assess the oxygen supplementation (>3L/min) duration compared to {Standard of care + placebo} treated group.

- *Number of days of oxygen supplementation in both treatment groups.*

To assess the hospital stay duration in both treatment groups for patients hospitalized because of Covid-19 infection consequences compared to {Standard of care + placebo} treated group.

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		Type of Study	Efficacy, Safety Study
	– *Number of days at the hospital from admission to discharge in both treatment groups.* To evaluate the effect of ABX464 on miR-124 expression in whole blood (PAXgene®) vs placebo (in selected sites and in hospitalized patients). – *Change from baseline in microRNA-124 levels in total blood (PAXgene®) at D0, D7 and D28 in both treatment groups.* To assess the change over time in CRP, Troponin I & T and D-dimer levels compared to {Standard of care + placebo} group. – *AUC and % of change from enrolment in CRP, Troponin I & T and D-dimer levels in both treatment groups.* To evaluate the prevention of Covid-19 related deaths compared to {Standard of care + placebo} group – *Time to death (log rank) and mortality rate (all causes, and Covid-19 related) in both treatment groups.* To evaluate SARS-CoV-2 infection in subjects during the course of the study compared to {Standard of care + placebo} group. – *SARS-CoV-2 virus in nasopharyngeal sample and/or in blood at Day 0, 7 (hospitalized patients), 14, 21, and 28.* To evaluate outpatients SpO_2 evolution from D0 to D14 – *Change in SpO_2 values from D0 to D14 in the outpatient's population in both treatment groups.* To evaluate the safety of ABX464 in study patients. – *Number and rates of participants with Treatment Emergent Adverse Event* – *Cumulative incidence of serious adverse events (SAEs) - 28 days* – *Cumulative incidence of Grade 3 and 4 adverse events (AEs) - 28 days* – *Number of participants with a discontinuation or temporary suspension of study drugs (for any reason) - 28 days.* ***Exploratory criteria***: To assess the radiological findings for patients hospitalized because of Covid-19 infection consequences. – *Central blinded review of the hospitalization discharge CT-Scans for descriptive analysis with regards to the disease severity and outcomes.*		
Main Selection Criteria	**Inclusion criteria:** **A patient will be eligible to participate in this study if ALL the following criteria are met:** 1. Adult (≥ 18 years old) men or women, hospitalized or not hospitalized, diagnosed for SARS-CoV-2 infection by PCR, with at least one associated risk factor. Considered risk factors are: • Age ≥ 65 years • Obesity defined as BMI ≥ 30 • Recent history of uncontrolled High Blood Pressure (SBP > 150 mm Hg & DBP >100 mm Hg) according to investigator • Treated diabetes (type I or II) • History of ischemic cardiovascular disease		

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2. Symptomatic patients at enrollment. Symptoms are defined as fever (body temperature ≥ 37.8 °C oral/tympanic, or ≥ 38.2 °C rectal) for more than 24 hours associated either with headache, sore throat, dry cough, fatigue, chest pain or choking sensation (with no associated respiratory distress), myalgia, anosmia or ageusia.
3. Patients with pulse oximetry arterial saturation (SpO2) ≥ 92 % on room air at enrolment.
4. Patients with the following hematological and biochemical laboratory parameters obtained within 7 days prior to D0:
   - Hemoglobin > 9.0 g dL^{-1}
   - Absolute Neutrophil Count ≥ 1000 mm^{-3};
   - Platelets ≥ 100,000 mm^{-3};
   - Creatinine clearance ≥ 50 mL min-1 by the Cockcroft-Gault formula
   - Total serum bilirubin < 2 x ULN
   - Alkaline phosphatase< 2 x ULN, AST (SGOT) and ALT (SGPT) < 3 x ULN;
5. Women of child bearing potential 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 enrolment. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (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 patient. 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 patients must not be planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male patients should use condom during the trial and for 6 months (180 days) post completion of their participation in the study. Male patients must not donate sperm as long as contraception is required. *For the purpose of this protocol, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation 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.*
6. Patients must understand, sign and date the written voluntary informed consent form at the visit prior to any protocol-specific procedures.
7. Patients able and willing to comply with study visits and procedures as per protocol.
8. Patients should be affiliated to a social security regimen (for French sites only).

Exclusion Criteria:

Patients who meet any of the following exclusion criteria will be excluded from the study:

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		Type of Study	Efficacy, Safety Study
	1. Patients with moderate or severe acute respiratory failure or requiring non-invasive ventilation or oxygen or with SpO2 < 92% or tachypnea (respiratory rate ≥ 30 breaths/min). 2. Patients treated with immunosuppressors and/or immunomodulators (cf. Appendix #2). 3. Engrafted patients (organ and/or hematopoietic stem cells). 4. Patients with uncontrolled auto-immune disease. 5. Patients with known or suspected active (i.e. not controlled) bacterial, viral (excluding COVID-19) or fungal infections. 6. Patients with preexisting, severe and not controlled organ failure. 7. History or active malignancy requiring chemotherapy or radiation therapy (excluding 2 years disease free survivor patients). 8. Pregnant or breast-feeding women. 9. Illicit drug or alcohol abuse or dependence that may compromise the patient's safety or adherence to the study protocol. 10. Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer. 11. Hypersensitivity to ABX464 and/or its excipients. 12. Any condition, which in the opinion of the investigator, could compromise the patient's safety or adherence to the study protocol.		
Medications	**Mandatory Medications** ▪ ABX464 or its matching placebo administered once daily with food. **Prohibited Concomitant Medications:** ▪ Immunosuppressors and/or immunomodulators (cf. Appendix #2). ▪ Drugs that could interact with ABX464 should be avoided especially the CYP1A2 substrates (cf. Appendix #1). The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (clozapine, theophylline, ropinirol, warfarin and methadone). In case of concomitant treatment with ondansetron the maximal daily dose must be limited to 8 mg. ▪ Inhibitors or inducers of the CYP1A2 (cf. Appendix #1). ▪ Use of any investigational or non-registered product within 3 months or within 5 half-lives before baseline, whichever is longer.		
Premature trial discontinuation	Patient's premature trial discontinuation must occur for the following reasons: ▪ Investigator's decision. ▪ An Adverse Event or an intercurrent condition that preclude continuation of treatment, o Specifically, an elevation ≥ 2.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or Alkaline phosphatase or in total bilirubin compared to baseline requires close observation with repeating liver enzymes and serum bilirubin tests every two days. Discontinuation of the study treatment should occur if: • ALT or AST > 8 x ULN; • ALT or AST > 4 x ULN <u>and</u> total bilirubin > 2 x ULN or INR>1.5; • ALT or AST > 4 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). ▪ Major protocol violation, ▪ Withdrawal of consent. ▪ Administrative reasons from the Sponsor.		
Patient Follow-up	At D28, the end of ABX464 treatment, patients will be invited to return for a follow-up visit at D49 which will constitute the End of Study visit.		

Study n°	ABX464-401	**Clinical Phase**	2/3
		Type of Study	Efficacy, Safety Study
	After EoS visit, patients will exit the study and will be treated/follow-up according to the site standard of care.		
Sample Size calculation	The primary efficacy endpoint is the rate of patients who do not require oxygen supplementation (>3L/min) or non-invasive mechanical ventilation (IMV and NIV, respectively) and who are alive at the end of the 28 days period. The primary endpoint will be compared between patients who received {Standard of care + ABX464} and {Standard of care + placebo}. For the sample size calculation, the following assumptions will be made: • Response rate (ABX464): 83 % • Response rate (placebo): 75 % • Type 1 error: 5% two-sided. Power: 80% • 2:1 (ABX464 50mg: placebo) study treatment allocation ratio. If the above assumptions hold true, then a total sample size of 897 patients will be required to be randomized (598 in the AX464 treatment group and 299 in the placebo group). It is assumed that 15% of patients will drop out prior to D28; leading to a total sample size of 1034 patients (690/344).		
Statistical Methods	**Interim analysis:** Interim safety or efficacy analysis(es) may be performed in this study based on DSMB and/or study Steering Committee recommendations. **Efficacy:** The primary efficacy endpoint will be analyzed by likelihood ratio chi-square test. Descriptive statistics will be presented by treatment arm for all secondary efficacy variables for each measurement timepoint. Continuous variables: mean, standard deviation, minimum and maximum, 95% confidence intervals, median and quartiles will be presented when considered relevant. Categorical variables: Counts, rates and 95% CIs will be calculated. Time-to-event variables will be analyzed by Kaplan-Meier plots. In addition, an attempt will be made to compare the study groups in respect of changes from baseline in different measurements by mixed model analysis of covariance. **Safety:** Analysis of safety will be performed on the safety data set consisting in all patients who received at least one dose of ABX464 in the study. The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the “CTC-AE” (Version 5.0) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and PCSAs [potentially clinically significant abnormalities (PCSAs) determined upon investigator considerations]. Adverse events will be tabulated (counts and percentages) by group. All adverse events will be listed, and the data will be tabulated by body system/organ class. Adverse event tabulations will include all treatment emergent adverse events, which will be further classified by severity, and relationship to treatment. Clinical laboratory parameters, vital signs, ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). The number of patients with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables by group.		
End of trial definition	The study will end once all the recruited patients have performed their safety follow-up and the End of Study visit, and all the data have been analyzed and computed in the clinical study report (CSR). As per the current study schedule, the CSR should be issued in Q1 2021.		

1. INTRODUCTION AND STUDY RATIONALE

1.1. SARS-CoV-2 infection

Coronaviruses are a large family of viruses that are known to cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).

A novel coronavirus SARS-CoV-2 (previously known as 2019-nCoV) was identified in 2019 in Wuhan, China. This is a new coronavirus that has not been previously identified in humans. The precise etiology is unknown and therefore medical therapy to cure the disease is not yet available.

The coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by this novel coronavirus, that shows sustained human-to-human transmission, and has been exported around the globe to reach pandemic proportion (1). The World Health Organization (WHO) officially declared the COVID-19 pandemic as a public health emergency of international concern. The novel coronavirus uses the same cell surface receptor, angiotensin-converting enzyme 2 (ACE2) as SARS-CoV, for entry, and infects preferentially the respiratory tract where this receptor is expressed (2). The elderly and people with underlying diseases are most prone to serious outcomes, which appear to be associated with acute respiratory distress syndrome (ARDS) and cytokine storm syndrome (1).

1.2. Management of patients

Two therapeutic strategies are currently being explored:

- To limit the spread of the COVID-19 infection by blocking the replication of the virus. This may be achieved through inhibition of the viral RNA dependent polymerase (RdRp) or by preventing the entry of the virus into pulmonary target cells or by serotherapy using immunized patient's plasma,
- To dampen the body's inflammatory response in the pulmonary tract.

Antiviral drugs for managing infection with human coronaviruses are not yet approved, posing a serious challenge to current global efforts aimed at containing the outbreak of COVID-19. Companies, including Gilead and AbbVie, are testing antiviral combination therapy, especially nucleoside analogues to block RdRp, and protease inhibitors in clinical trials, in order to block the entry of the virus into cells. Chloroquine is being evaluated based on its ability to block viral processes and maturation.

Several companies, including Sanofi, Abbvie, Roche/Genetech, are testing monoclonal antibody therapy to block the inflammatory response by inhibiting individual inflammatory receptor pathways.

Additional therapies focused on thromboembolic complications and standard intensive care treatments are also being studied.

The response to each of these therapies is highly uncertain and, given the scope of this pandemic, other treatment options that more broadly target the immune "Cytokine Storm" syndrome must urgently be explored in well-designed clinical trials.

1.3. Study rationale

Developed initially as an inhibitor of HIV replication (3-5) and HIV reservoir reduction (6), ABX464 binds to the Cap Binding Complex (CBC) that regulates splicing and export of mRNA from the nucleus (3). ABX464-CBC interactions were shown to strengthen the RNA quality control of HIV-RNA biogenesis preventing the production of unspliced HIV RNA (3), thereby reducing the viral reservoirs of HIV infected patients (6).

While capable of directly altering the splicing of ~0.1% of transcripts in cells, the examination of the effects of ABX464 on the microRNA population using the Affymetrix Genechip microRNA array 2.0, and a TaqMan® Array Human microRNA for confirmation, showed that the selective expression of a single microRNA was significantly increased by ABX464: miR-124 (7).

MicroRNAs are small noncoding RNAs that regulate gene expression by binding to the 3′ UTR of their target mRNAs to induce translational repression and mRNA deadenylation and decapping (8). As a result, microRNAs reduce expression of target genes by increasing degradation of the respective RNA and/or inhibiting their translation into proteins. Often, microRNAs regulate sets of genes belonging to the same pathway.

miR-124 is transcribed from 3 genomic loci, locus 1 (exonic), locus 2 (monocistronic) and locus 3 (monocistronic). Studies have demonstrated that ABX464 induces miR-124 expression from locus 1 only. Locus 1 contains the long

non-coding RNA, lncRNA00599-205 from which miR-124 is derived by splicing. Mutation of the splice sites of lncRNA00599-205 prevented the overexpression of miR-124 with ABX464 treatment (7).

The RNA targets of miR-124 have been shown to be related to the cytokine and pro-inflammatory response of innate immune cells, especially tissue-resident macrophages. The JAK-STAT pathway that is downstream of cytokine signaling is affected by miR-124, especially STAT3 (9), as is NFkB, the master transcription factor of pro-inflammatory responses (10). In addition, miR-124 has been shown to have a direct effect on the translational downregulation of MCP-1, monocyte chemoattractant protein (11), as well as the IL-6 receptor (10). In conjunction with these effects, the increase of miR-124 has been associated with the maintenance of the M2 differentiation of the tissue-resident macrophage. Indeed, M2 macrophages control tissue inflammation by producing type 2 cytokines such as IL-4 and IL-10, two mediators of tissue homeostasis (12). In summary, miR-124 is anti-inflammatory by reducing protein levels of these pro-inflammatory pathways, and also anti-proliferative by affecting some of the important cell cycle transcripts (10).

In the mouse model of Dextran Sodium Sulphate (DSS) exposure in which colonic inflammation is triggered, ABX464 demonstrated a marked decrease in the inflammatory colitis (13, 14). This effect was associated with prevention of proliferation of Th17 cells in both peripheral blood and mesenteric lymph nodes. Th17 cells, the CD4+ T-cell subset that produces interleukin-17 (IL-17) and are pro-inflammatory and are dependent on STAT3 for proliferation (15, 16). IL-17 is a highly inflammatory cytokine with robust effects on stromal cells in many tissues. ABX464 showed also efficacy in animal models related to rheumatoid arthritis (CIA mice model) as well as a good bioavailability in lung tissues.

1.4. Investigational treatment description

ABX464 is a novel, oral, safe and potent anti-inflammatory drug candidate, with impressive Phase 2a clinical results in ulcerative colitis. As described above, the drug candidate is in a Phase 2b clinical trial in Europe, Canada and in the US (IND 141396).

More than 300 patients have been treated with ABX464 with a good safety profile; some patients have received ABX464 for over 2 years.

ABX464 selectively up-regulates a microRNA, mir-124, a physiological negative regulator of inflammation, that acts on several key pathways of inflammatory cytokines signaling, especially STAT3 (Signal Transducers and Activators of Transcription). Indeed, many Covid-19 patients develop acute respiratory distress syndrome (ARDS), which leads to pulmonary edema and lung failure (20). Elevated pro- inflammatory cytokines involved in Th17 responses in COVID-19 infected patients may be the cause of vascular permeability and leakage (21). Attenuation of Th17 proliferation, in addition to its inhibition of inflammatory cytokines, by ABX464 could be a way to prevent the severe acute respiratory syndrome-related caused by Covid-19 infection.

ABX464 has the potential to alter the clinical course of Covid-19 infection by limiting the body's cytokine-mediated inflammatory response (cytokine storm).

1.4.1. Investigational product description

The chemical name of ABX464 molecule is 8-chloro-N-[4-(trifluoromethoxy) phenyl]quinolin-2-amine, or (8-chloro-quinolin-2-yl)-(4-trifluoromethoxy-phenyl)-amine. Its molecular weight is 338.7.

The study drug is formulated as hard gelatin, powder-filled capsules (size 1).

1.4.2. Investigational product Mode of Action

The mechanism of action of ABX464 in inflammatory conditions is mediated throughout the observed effect on miR-124 observed in vitro and in patients. ABX464 in a DSS mice model has no effect on the expression profile of cytokines and chemokine signaling pathways in the absence of DSS exposure. In the presence of DSS, ABX464 compensated for most of the expression differences induced by DSS exposure, which suggests that ABX464 restores the transcriptional program modified by DSS in the colon. In addition, in the DSS model, ABX464 leads to reduced expression of anti-inflammatory cytokines: IL-6 (2x), TNF (7.5x) and MCP-1 (6x).

In-Vitro assays

- *Modulation of miR-124 by ABX464*

Study ABX464PHA011 performed in humans PBMCs ad monocyte-derived macrophages (huMDM)revealed that both ABX464 and its primary metabolite ABX464-N-Glu induced a significant increase in miR-124 expression. MiR-

124 appears to regulate the expression of signal transducer and activator of transcription 3 (STAT3). MiR-124 has also been shown to be required for the protective role of nicotine in DSS colitis mice.

- *Cytokines/chemokine modulation in huMDM*

ABX464 and ABX464-N-Glu treatment induced a significant decrease in pro-inflammatory proteins in HuMDM (IL-6, TNFa, IL-1b), but has no significant effect on the active form of IL-12 and IFNg. ABX464 and ABX464-N-Glu treatment resulted in a decrease of expression of adhesion and migration proteins (ICAM-1: responsible for tissue transmigration of leukocytes, MIF: responsible for inhibiting macrophage migration). More importantly, chemokines CXCLI (neutrophil chemoattractant activity) and the CCL2/MCP-1 (chemokine monocyte chemoattractant protein-1) are also significantly reduced. Down-regulation of CCL2 is associated with up-regulation of miR-124. ABX464 and ABX464-N-Glu up-regulate miR-124 and thus may explain their anti-inflammatory effects.

In-Vivo assays

- *DSS mice model*

ABX464 and its primary metabolite, ABX464-N-Glu were tested in a mouse model of colon inflammation. This study tested the protective properties of ABX464 in a DSS-induced experimental model of colitis.

In this model inflammation is specifically induced in the colon via the administration of DSS in drinking water for approximately 5-8 days. ABX464 was administered for 8 days via gavage. These results showed that DSS-induced weight loss, an established symptom of intestinal injury, was significantly reduced in mice receiving ABX464 (Figure 2). This induced intestinal inflammation is usually strongest 3 days after the termination of the DSS challenge. The weight of ABX464-treated mice had already returned to pre-treatment levels at that time point, and the mice displayed decreased disease parameters such as smaller and fewer colonic lesions as well as decreased shrinkage of colon length. Importantly, ABX464 did not affect the colons of mice not exposed to DSS. Noteworthy, the disease dampening influence of ABX464 in DSS-colitis was observed in experiments performed in different animal facilities, suggesting that this phenomenon is not dependent on a particular intestinal flora.

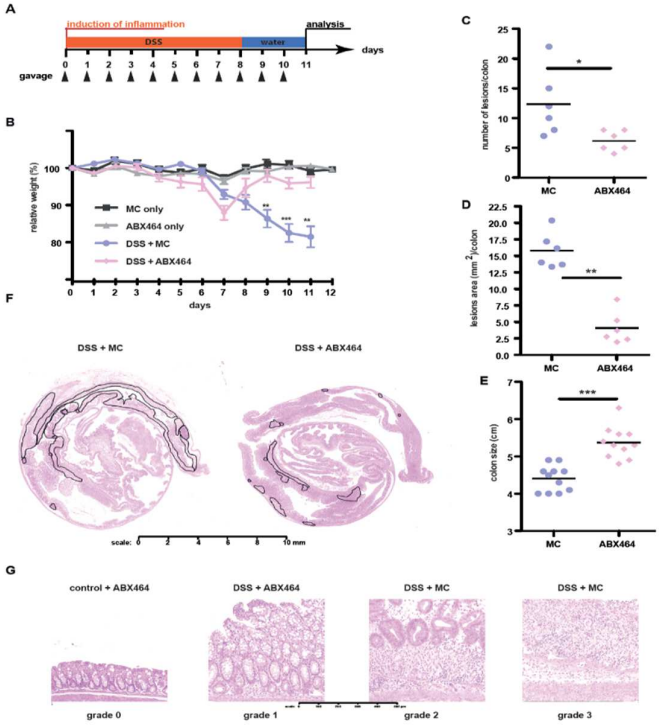


Figure 2: ABX464 treatment suppresses disease severity in DSS-induced colitis. (A) C57BL/6 mice (n=12 each cohort) Subjected to the DSS colitis protocol shown received orally once a day ABX464 (50 mg/kg) in methylcellulose or methylcellulose only through gavage. **(B)** Weight development in ABX464 and methylcellulose (MC) only treated mice during DSS-induced colitis. Control cohorts included mice not exposed to DSS. **(C, D, E)** At the end of the protocol described in A mice (n=6 or n=11) were sacrificed and colons were analyzed by histology for colitis severity including number of lesion (C), lesion size (D) and colon size (E). **(F)** Representative images of hematoxylin and eosin staining of paraffin-embedded colon sections prepared as "Swiss rolls". Single lesions are delimited by black lines. **(G)** Representative images of lesions with different pathological grade according to Hao et al. Grade 1: Immune cell infiltration in lamina propria (LP); intact epithelial barrier and GI structure. Grade

2: Immune cell infiltration in LP; crypt distorsion or loss; gobelet cell loss; intact, but abnormal epithelial barrier. Grade 3: Immune cell infiltration in LP and submucosa; epithelial barrier loss and ulceration/necrosis.

Abivax tested whether the protective effect of ABX464 is maintained during prolonged DSS exposure (Figure 3A), which typically is lethal for mice. However, the daily application of ABX464 allowed the mice to be exposed to DSS for at least 63 days. Following a moderate initial body weight loss of approximately 5%, the mice recovered and maintained their initial body weight (Figure 3B). The mice that received ABX464 for only the first 20 days during the prolonged DSS exposure displayed similar body weight development and survival rates to those that received ABX464 for the entire study. Nevertheless, the colons of these two mouse cohorts displayed significant differences when examined for histopathological parameters including lesion size (Figure 3 C D). This finding suggests that the 20-day administration of ABX464 provided a partially protective effect that was maintained for the duration of the 63-day DSS challenge.

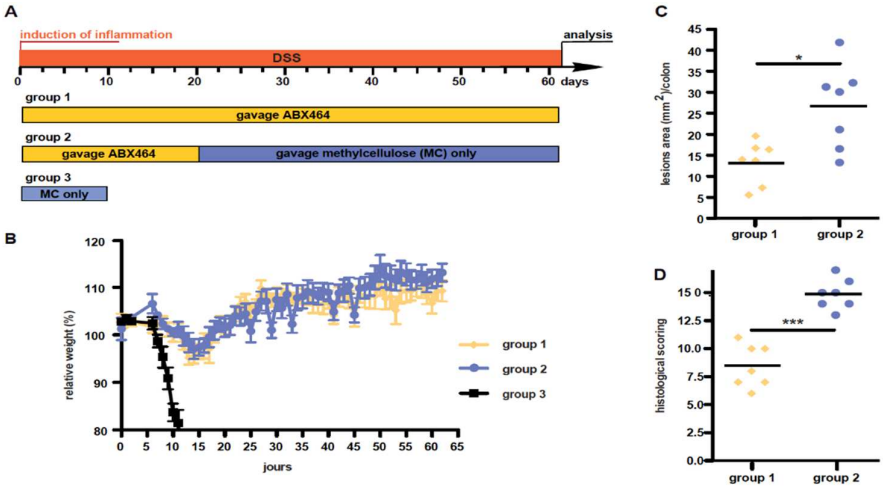


Figure 3: The protective effect of ABX464 is maintained in mice during continuous DSS-treatment. (A) C57BL/6 mice (n=8 each cohort) were challenged with DSS for 63 days. Mice received orally once a day ABX464 in methylcellulose during the whole protocol (group 1) or only for the first 20 days followed by methylcellulose only administration (group 2). Mice of group 3 received methylcellulose during DSS-treatment and had to be scarified at day 10. **(B)** Weight development in ABX464-treated mice during DSS-administration. **(C, D)** Colons were analyzed by histology for lesion size (C) and colitis severity (D) at the end of the protocol. Histological scoring was performed as stated above.

In humans, ABX464 is rapidly metabolized into one main metabolite, ABX464-N-Glucuronide. (ABX464-N-Glu). Thus, ABIVAX studied in the same DSS-mice model the efficacy of the ABX464-N-Glucuronide. Like ABX464, in the same DSS-mice model, ABX464-NGlu (40 mg/kg) protects mice from DSS-induced weight loss (Figure 53). This finding has substantial implications in light of treating inflammatory ulcerative colitis (UC) disease since studies in healthy patients demonstrated that:

- ABX464-NGlu C_{max} was approximately 160-fold higher than those of ABX464 and had a much longer $t_{1/2}$ (90 to 110 hours) than the parent compound (2-3 hours), resulting in a > 1000-fold difference in AUC between the 2 compounds.
- The markedly higher plasma concentrations of ABX464-N-Glu, and its ability to protect mice from DSS-induced colitis, may allow the use of lower doses of the parent compound ABX464 for a longer period in UC patients.

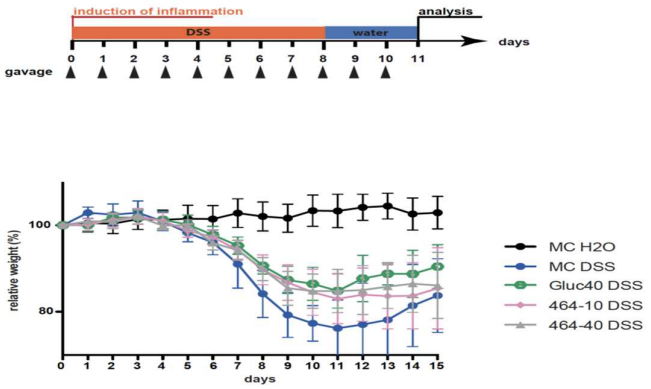


Figure 4: ABX464-N-Glu treatment suppresses disease severity in DSS-induced colitis. (A) C57BL/6 mice (n=10 for DSS and-n=9 for DSS + ABX464 and for DSS + ABX464 N-Glucuronide subjected to the DSS colitis protocol shown received orally once a day ABX464 40 mg/kg (DSS + ABX464, in green), or ABX464-N-Glucuronide 40 mg/kg (DSS + ABX464 N-Glucuronide, in orange) in methylcellulose or methylcellulose only (DSS, in red) through gavage. **(B)** Weight development in ABX464, in ABX464-N-Glu and methylcellulose only treated mice during DSS-induced colitis

Taken together, these *in-vivo* studies demonstrated the potency of the drug candidate ABX464 to dampen intestinal inflammation in DSS-treated mice (Figure 4). Through this anti-inflammatory effect, ABX464 might be able to modulate important disease parameters in both HIV and inflammatory ulcerative colitis (UC) disease because it demonstrates long-lasting control of the HIV-virus in humanized mice as well as the critical features of DSS-induced colitis.

- *CIA mouse model*

In order to assess the activity of ABX464 on rheumatoid arthritis, DBA-1 mice were exposed to the CIA model. Bovine collagen II was injected in intradermic on the base of the tail at two different sites of injection (100µg in 100µl, dissolved in Acetic acid 0.05M and emulsified with Freund Complete adjuvant CFA 1:1) at day 0 (W0) and day 21 (W3). The 4 paws were measured using a caliper sagitally. A mean of the 4 paws is calculated. The development of arthritis is considered if this mean paw thickness exceeded 2 mm on two consecutive measures. The measures are performed every 2 to 3 days from the 5th week following the 1st injection of CFA + bovine collagen II (W5).

The incidence of arthritis was drastically reduced in the ABX464 groups, as assessed by arthritis-survival free curves. The average of joint thickness observed at week 12 following the 1st injection of bovine collagen and CFA (21 weeks of age) was reduced in ABX464 groups compared to MC or H20 groups (4 A and B, phase 1). The median [IQR] joint thickness was 0.19 cm [0.18-0.20] in ABX464 vs 0.21 [0.19-0.23] in MC (Mann-Whitney p=0.06) and for INF006002, median [IQR] joint thickness was 0.19 cm [0.18-0.20] in ABX464 vs 0.21 [0.19-0.22] in MC 0.20 [0.19-0.22] in H20 groups (Kruskall-Wallis p=0.002).

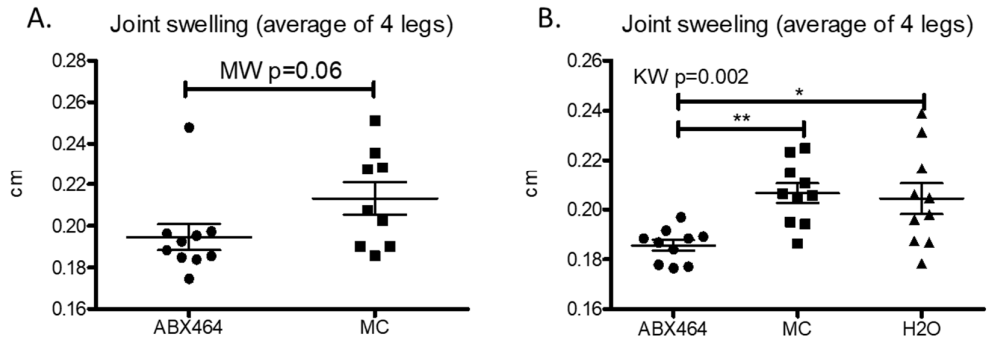


Figure 5. Study DBA1 Joint swelling development in mice.

Mean thickness of joints (mean of 4 paws) measured at week 12 (21 weeks of age) in INF006001 (A) and INF006002 (B). Mann-Whitney test performed in A and Kruskall-Wallis with post-hoc Dunn's analysis in B.

In this study, we have found a specific effect of ABX464 on Collagen Induced Arthritis (CIA). The daily contribution of 40mg/kg of ABX464 in “per-os” allows to reduce significantly with two independent experiments the inflammation noticed by joint swelling in this model.

1.5. Non-Clinical background information

The toxicity of ABX464 and ABX464-N-Glu was studied in a range of rodent and nonrodent species (rats, rabbits, dogs, cynomolgus and marmoset monkeys, and mini-pigs) with treatment durations ranging from 2-weeks to 6/9 months. These studies have demonstrated that ABX464 and ABX464-N-Glu are overall well tolerated. Vomiting and ptyalism were the major clinical signs, and the main target organs of ABX464 toxicity were the gastro-intestinal tract and the liver. The adverse effects noted on these organs were essentially mild/moderate but showed reversibility during the recovery phases.

ABX464 was found to be non-genotoxic. Its main metabolite, the ABX464-N-Glu was not mutagenic as assessed by an Ames test, an in vitro and an in vivo micronucleus assay.

Reproductive toxicity was assessed from fertility to postnatal development, in five studies. In rabbits, the maternal NOAEL was considered to be 9mg/kg od. and the NOAEL for the embryo-fetal development less than 1mg/kg od. In rats, the maternal NOAEL and the NOAEL for pup development and survival is considered to be lower than 15 mg/kg od. The F1 generation NOAEL is considered to be 40mg/kg od. in absence of adverse effect at this dose-level.

In minipigs the main adverse finding was centrilobular hepatocellular degeneration/necrosis associated with hemorrhage, fibrosis and /or extramedullary hematopoiesis observed at dose levels of 10mg/kg and above. The liver lesions observed in the single animal administered 5mg/kg od, were not considered adverse. Based on this observation, the NOAEL is 5mg/kg od.

No signs of hepatotoxicity have been observed in any of the patients treated with ABX464 in the previously conducted or on-going clinical trials. ABIVAX and its clinical experts consider that patients treated with ABX464 are not at increased risk of developing a drug-induced hepatotoxicity. Nevertheless, a specific liver function monitoring plan has been implemented in the current clinical study.

Regarding the other observations made from the pre-clinical toxicology program, please refer to the current version of the Investigator’s Brochure.

1.6. Previous clinical experience with ABX464

ABX464 has been tested in healthy volunteers, patients with HIV infection and in patients with ulcerative colitis. miR-124 was shown to be up-regulated in all ABX464-treated subjects tested during the clinical program, and all patients came back to pre-dosing levels once the administration of ABX464 was stopped. To date, more than 300 subjects have received ABX464 in completed and ongoing clinical trials, and the results have shown a favorable safety profile and no serious adverse drug reactions.

ABX464 has completed a Phase 2a induction study (Study ABX464-101) in patients with moderate to severe ulcerative colitis. The results showed a rapid onset of clinical improvements, including efficacy in patients resistant to prior treatment with biologics. The subsequent long-term open-label maintenance study showed impressive 12-month data which were presented during the United European Gastroenterology Conference (UEG), Barcelona on October 21st, 2019 by Prof. Severine Vermeire, M.D., Ph.D., Head of the IBD Center at the University Hospitals Leuven, Belgium.

19 of 22 patients completed one year of open-label maintenance. Patients showed continued improvement as demonstrated by a 78% reduction of Total Mayo Score, 89% reduction of endoscopic subscore and 97% reduction of fecal calprotectin biomarker (normalized). Endoscopy at Month 12 was performed in 16 / 19 patients, of whom 12 (75%) achieved clinical remission. A continued good long-term safety profile was observed, with no reported serious adverse drug reactions as of the annual safety reporting cut off-date (31 October 2019).

In summary, the impressive efficacy seen in the 8 weeks induction study was not only durable, but even substantially improved in this one-year maintenance study, with 75% of the patients with endoscopy having achieved a clinical remission.

Furthermore, the following studies have been initiated: i) a phase 2b study has been initiated in 232 patients with moderate to severe ulcerative colitis, and ii) a phase 2a study in 60 patients with rheumatoid arthritis. A Phase 2b study in patients with Crohn’s Disease is planned.

For further information, please refer to the current Investigator’s Brochure for Covid-19.

1.7. Dose justification

ABX464 administered at 50mg QD is safe and efficacious in patients suffering from moderate to severe Ulcerative Colitis. Over 300 patients have safely been exposed to ABX464, some of them for more than 2 years. Thus, 50mg QD may be the appropriate dose for use in inflammatory conditions including the Cytokine Storm which is observed in some COVID-19 patients. Indeed, this regimen has been shown to lead to statistically significant upregulation of the mir-124 which is the cornerstone of the mode of action of ABX464.

In addition, ABX464 has recently been tested in primary pulmonary cells infected by with SARS-CoV-2 (MucilAir cells). At 48h post infection, the viral load measured in the supernatant by qPCR was reduced by 1 log with ABX464 and even 2 logs with its active metabolite: ABX464-N-glucuronide.

Table 1. Percentage of inhibition induced by ABX464 or its main metabolite ABX464-N-Glu.

	% of viral inhibition (mean; n=2)
ABX464 0.1 µM	32,45 %
ABX464 1 µM	93,25 %
ABX464 5 µM	95,54 %
ABX464-N-Glu 0.1 µM	No inhibition
ABX464-N-Glu 1 µM	29,00 %
ABX464-N-Glu 10 µM	87,95 %

Based on day 1 human pk plasmatic data (cmax), the concentration range used in this assay is achievable in human using the 50mg qd dose (abx464: ≈0.2 µm and abx464-n-glu ≈5 µm). Thus, this 50 mg qd dose regimen is deemed sufficient to provide efficacy both from an antiviral and anti-inflammatory perspectives.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary objective and endpoint

The primary objective of the study is to determine the efficacy of ABX464 50mg to prevent respiratory failure or death in study patients.

- *Rate of patients who do not require use of high-flow oxygen (use of high-flow oxygen being defined as settings of 3 L/min or greater AND with at least one SpO2 measurement < 92%, with or without O2 supplementation) or non-invasive mechanical ventilation (IMV and NIV, respectively) within 28 days and who are alive at the end of the 28 days period.*

2.2. Secondary objectives and endpoints

The secondary objectives are:

To evaluate the proportion of patients requiring hospitalization during the study compared to the {Standard of care + placebo} group

- *Rate of patients hospitalized in both treatment groups*

To assess the proportion of patients reporting each severity rating on a 7-point ordinal scale during the course of the study compared to the {Standard of care + placebo} group

- *Percentage of patients reporting each severity rating on a 7-point ordinal scale at each study visit (i.e. Not hospitalized, no limitations on activities; Not hospitalized, limitation on activities; Hospitalized, not requiring supplemental oxygen; Hospitalized, requiring supplemental oxygen; Hospitalized, on non-invasive ventilation or high flow oxygen devices; Hospitalized, on invasive mechanical ventilation or ECMO; Death);*

To assess the time to an improvement of one category of the 7-point on an ordinal scale from baseline, compared to the {Standard of care + placebo} groups

- *Mean change in the ranking on an ordinal scale from baseline to days 7, 14, 21, and 28*

To evaluate and compare the effect of ABX464 on oxygen saturation before hospitalization

- *% change and AUC over time of oxygen saturation measured by daily pulse oximetry before hospitalization*

To evaluate and compare the effect of ABX464 on oxygen saturation level at the end of the study treatment

- *Rate of patients with SpO2 ≤94% and rate of patients with SpO2 ≤92% at Day 28*

To evaluate and compare the effect of ABX464 on immunophenotyping (in selected sites only) and cytokines levels during the study in hospitalized patients enrolled in both treatment groups.

- *Change from enrolment in inflammatory markers in plasma (i.e. MCP-1, MIP-1 α, G-CSF, IL-1b, IL-2, IL-6, IL-7, IL-10, IL-17, INFg and TNFa) and in immune phenotype and assessment of cell-activation markers in PBMCs at D14, D28 for hospitalized patients only.*

To evaluate the proportion of patient requiring oxygen supplementation (>3L/min) during the study compared to the {Standard of care + placebo} group.

- *Rate of patients requiring oxygen supplementation in both treatment groups.*

To assess the time to hospitalization (all causes and Covid-19 related hospitalization) during the study compared to {Standard of care + placebo} treated group.

- *Time to hospitalization (log rank) from baseline in both treatment groups.*

To evaluate the time to application of *invasive and non-invasive mechanical ventilation (IMV and NIV, respectively) or high flow oxygen therapy* excluding simple oxygen supplementation) and oxygen supplementation during the study compared to {Standard of care + placebo} treated group.

- *Time to assisted ventilation and oxygen supplementation (log rank) from baseline in both treatment groups.*

To assess the IMV and/or NIV duration compared to {Standard of care + placebo} treated group.

- *Number of days of assisted ventilation in both treatment groups.*

To assess the oxygen supplementation (>3L/min) duration compared to {Standard of care + placebo} treated group.

- *Number of days of oxygen supplementation in both treatment groups.*

To assess the hospital stay duration in both treatment groups for patients hospitalized because of Covid-19 infection consequences compared to {Standard of care + placebo} treated group.

- *Number of days at the hospital from admission to discharge in both treatment groups.*

To evaluate the effect of ABX464 on miR-124 expression in whole blood (PAXgene®) vs placebo (in selected sites and in hospitalized patients).

- *Change from baseline in microRNA-124 levels in total blood (PAXgene®) at D0, D7 and D28 in both treatment groups.*

To assess the change over time in CRP, Troponin I & T and D-dimer levels compared to {Standard of care + placebo} group.

- *AUC and % of change from enrolment in CRP, Troponin I & T and D-dimer levels in both treatment groups.*

To evaluate the prevention of Covid-19 related deaths compared to {Standard of care + placebo} group

- *Time to death (log rank) and mortality rate (all causes, and Covid-19 related) in both treatment groups.*

To evaluate SARS-CoV-2 infection in subjects during the course of the study compared to {Standard of care + placebo} group.

- *SARS-CoV-2 virus in nasopharyngeal sample and/or in blood at Day 0, 7 14, 21, and 28.*

To evaluate outpatients SpO_2 evolution from D0 to D14

- *Change in SpO_2 values from D0 to D14 in the outpatient's population in both treatment groups.*

To evaluate the safety of ABX464 in study patients.

- *Number and rates of participants with Treatment Emergent Adverse Event*
- *Cumulative incidence of serious adverse events (SAEs) - 28 days*
- *Cumulative incidence of Grade 3 and 4 adverse events (AEs) - 28 days*
- *Number of participants with a discontinuation or temporary suspension of study drugs (for any reason) - 28 days.*

Exploratory criteria:
To assess the radiological findings for patients hospitalized because of Covid-19 infection consequences

- *Central blinded review of the hospitalization discharge CT-Scans for descriptive analysis with regards to the disease severity and outcomes.*

3. INVESTIGATIONAL PLAN

3.1. Study design and methodology

This phase 2/3 study will evaluate the efficacy and safety of ABX464 50mg QD (oral capsule), on treating inflammation and preventing acute respiratory failure in patients infected with SARS-CoV-2.

Eligible patients will be randomized according to a 2:1 ratio into 2 treatment cohorts as follows:

- Standard of Care + Placebo cohort: 344 patients
- Standard of Care + ABX464 50mg QD: 690 patients

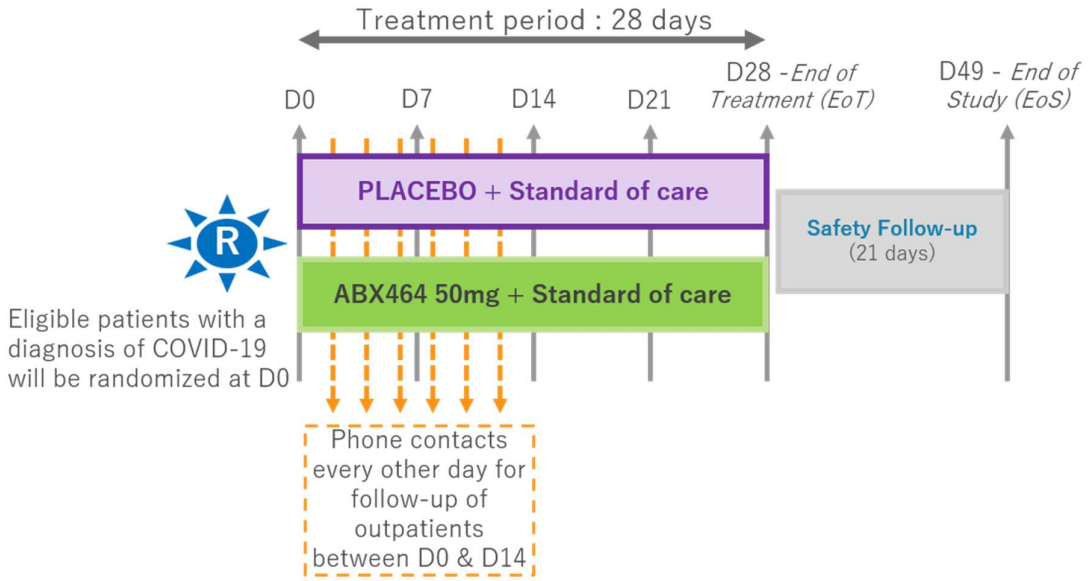
Upon randomization, patients will be stratified according to:

- Age ≥ 65 years *or* < 65 years (with at least one risk factor)
- Inpatient *or* outpatient, at the time of enrolment

Study design:

The study will consist of 2 periods:

- Treatment phase: randomized patients will be treated for 28 days
- Safety follow-up phase of 21 days after which the End of Study visit (EOS) will be performed.



From Day 0 onwards, randomized patients will be followed by the investigational site at 7 days (D7 +/- 2 days), 14 days (D14 +/- 2 days), 21 days (D21+/- 2 days) and finally 28 days (D28 +/- 2 days) after randomization. A long-term follow-up (3 months) looking at lung function is planned and will be part of an upcoming protocol amendment

Should a patient be hospitalized at D0, Day 7 visit will be an on-site visit.

Should a patient not be hospitalized, considering a quarantine period might be applied for infected patients, a remote medical monitoring will be performed by the investigator or his designee every 2 days from D0 and until D14. Every attempt to perform the Day 7 on-site visit should be made anyway. For outpatients, an oximeter will be provided at Day 0. During the remote medical monitoring, the patient will be asked to self-measure every day the oxygen saturation, body temperature and will be asked for any potential signs of COVID-19 infection worsening. Subsequent, D14, D21 and D28 will be on-site visits.

If no quarantine period is applied or if patients migration to the study site is acceptable as per local regulation, outpatients will perform a D7 visit on-site, and the same examinations as hospitalized patients will be performed.

3.2. Dose limiting toxicity (DLT)

A dose limiting toxicity (DLT) is defined as a grade 3 or higher adverse event as defined by the Common Terminology Criteria for Adverse Events (CTC-AE V5.0) considered by a safety review board as probably or definitely related to study treatment. Every grade 3 or higher adverse event will be immediately (within 48 hours) reported to the DSMB for causality assessment.

In case of a life threatening (grade 4) adverse reaction (i.e. probably or definitely related to study treatment) new enrolment and treatment of ongoing patients will be immediately discontinued. In that case, all safety data will be reviewed by DSMB members. Enrollment and treatment of new patients will be resumed upon DSMB recommendations and after regulatory approvals are obtained.

3.3. Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB), with expertise and experience in virology and immunology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee effective protection of patients, ensure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.

The DSMB will meet first after the 20 first patients are enrolled and treated for at least 4 weeks (D28) and then every month after this first meeting.

The DSMB will oversee the adequate balance of baseline characteristics (i.e. gender, disease duration, previous and concomitant CD medication) among the treatment groups and will review all potential causally-related Serious Adverse Events within 7 days of the initial notification by an investigating site.

The DSMB has a consultative role. It will inform the Sponsor who will decide whether the DSMB recommendation will be followed. Besides, the DSMB may recommend the early termination of the trial at any time if an unacceptable toxicity occurs.

A DSMB charter must be available upon submission of the trial (initial protocol) to the respective competent authorities.

3.4. Steering Committee

A study steering committee will oversight the practical aspects of the study especially with regards to the evolving nature of the COVD-19 infection.

The Steering Committee will work in conjunction with the DSMB. Specific responsibilities of the Steering Committee include, but are not limited to, the following: ensure the overall supervision of the Mir-Age study, take actions to reduce deviations from the protocol to a minimum, review of the progress of the study, make any recommendations for modifications to the protocol that might be medically or ethically relevant during the course of the study.

The Steering Committee will be able to terminate the trial if the medical relevance of the MiR-Age is substantially modified during its execution. ABIVAX and principal investigator will agree, in writing prior to the start of the study, to the charter of the Steering Committee.

3.5. Duration of study participation

There is no screening visit in the present protocol.

After the collection of the signed informed consent, patients will be treated for 28 days, then will go through a 21 days follow-up period that will take place after the last treatment dose administration.

Therefore, the total study duration for a given participant is up to 49 days.

4. STUDY POPULATION

4.1. Number of Patients/Centers

Approximately 1034 patients will take part in this study. These patients will be enrolled in up to 50 sites located in Europe (i.e. France, Germany, Belgium, The Netherlands, Italy, Spain).

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

A patient will be eligible to participate in this study if ALL the following criteria are met:

1. Adult (≥ 18 years old) men or women, hospitalized or not hospitalized, diagnosed for SARS-CoV-2 infection by PCR, with at least one associated risk factor. Considered risk factors are:
    - Age ≥ 65 years
    - Obesity defined as BMI ≥ 30
    - Recent history of uncontrolled High Blood Pressure
    - Treated diabetes (type I or II)
    - History of ischemic cardiovascular disease
2. Symptomatic patients at enrollment. Symptoms are defined as fever (body temperature ≥ 37.8 °C oral/tympanic, or ≥ 38.2 °C rectal) for more than 24 hours associated either with headache, sore throat, dry cough, fatigue, chest pain or choking sensation (with no associated respiratory distress), myalgia, anosmia or ageusia.
3. Patients with pulse oximetry arterial saturation (SpO2) ≥ 92 % on room air at enrolment.
4. Patients with the following hematological and biochemical laboratory parameters obtained within 7 days prior to D0:
    - Hemoglobin > 9.0 g dL-1
    - Absolute Neutrophil Count ≥ 1000 mm-3;
    - Platelets ≥ 100,000 mm-3;
    - Creatinine clearance ≥ 50 mL min-1 by the Cockcroft-Gault formula
    - Total serum bilirubin < 2 x ULN
    - Alkaline phosphatase< 2 x ULN, AST (SGOT) and ALT (SGPT) < 3 x ULN;
5. Women of child bearing potential 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 enrolment. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (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 patient. 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 patients must not be planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male patients should use condom during the trial and for 6 months (180 days) post completion of their participation in the study. Male patients must not donate sperm as long as contraception is required. *For the purpose of this protocol, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation 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.

6. Patients must understand, sign and date the written voluntary informed consent form at the visit prior to any protocol-specific procedures.
7. Patients able and willing to comply with study visits and procedures as per protocol.
8. Patients should be affiliated to a social security regimen (for French sites only).

4.2.2. Exclusion Criteria

Patients who meet any of the following exclusion criteria will be excluded from the study:

1. Patients with moderate or severe acute respiratory failure or requiring non-invasive ventilation or oxygen or with SpO2 < 92% or tachypnea (respiratory rate ≥ 30 breaths/min).
2. Patients treated with immunosuppressors and/or immunomodulators (cf. Appendix #2).
3. Engrafted patients (organ and/or hematopoietic stem cells).
4. Patients with uncontrolled auto-immune disease.
5. Patients with known or suspected active (i.e. not controlled) bacterial, viral (excluding COVID-19) or fungal infections.
6. Patients with preexisting, severe and not controlled organ failure.
7. History or active malignancy requiring chemotherapy or radiation therapy (excluding 2 years disease free survivor patients).
8. Pregnant or breast-feeding women.
9. Illicit drug or alcohol abuse or dependence that may compromise the patient's safety or adherence to the study protocol.
10. Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer.
11. Hypersensitivity to ABX464 and/or its excipients.
12. Any condition, which in the opinion of the investigator, could compromise the patient's safety or adherence to the study protocol.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1. Study Flow Chart

A detailed study flow chart (with all assessments) is displayed hereafter.

	TREATMENT PERIOD FOR INPATIENTS						UNSCH. VISIT	Safety FUp period
	V1	Remote Medical Monitoring of Outpatients to be done every 2 days between D0 and D14	V2	V3	V4	V5 - End of treatment		V6 - End of Study
	D0		D7 for hosp. Patients/and potentially outpatients	D14	D21	D28		D49
GENERAL								
Signed inform consent form collection	X							
Check of IN/EX Criteria	X							
Demographic data collection	X							
Medical History	X							
Current medications	X	X	X	X	X	X	X	X
PHYSICAL EXAMS								
Physical Examination (including vital signs) [1]	X		X	X	X	X	X	X
Oxymeter and patient diary dispensation/collection	X			X				
Remote monitoring of body temperature, SPO2 and Clinical Signs of COVID-19		Monitoring every 2 days between **D0 and D14**						
Body Weight (kg) & Height (cm) measurements [2]	X							
ECG [3]	X		X	X	X	X	X	X
ANALYSIS TO BE PERFORMED LOCALLY								
Blood Pregnancy test (WOCBP) [4]	X							X
Hematology + Biochemistry [5]	X		X	X	X	X	X	X
BIOBANKING								
Plasma (CRP, Troponin I & T, D-Dimer [6])	X		X	X	X	X	X	
Immunophenotyping and cells activation markers[7]	X			X		X	X	
Blood sample Cytokines[8]	X			X		X	X	
Nasopharyngeal and blood samples for viral load assessment	X		X	X	X	X	X	
Samples for miRNA-124 (Blood PAXgene tube)	X		X			X		
IMAGING								
Chest CT-SCANS [9]	(X)		*For hospitalized patients only*					
TREATMENT ALLOCATION								
Randomization	X							
ABX464/placebo treatment dispensation [10]	X							
ABX464/placebo treatment accountability						X		
SAFETY								
Adverse Events recording	X	X	X	X	X	X	X	X

[1] **Physical examinations:** a complete physical examination will be performed at D0, at the End of treatment visit (EoT), and at the End of Study visit (EoS). Only differences from baseline will be reported at every other visit
[2] **Body Weight and Height**: Body weight and height will be measured at D0 for BMI assessment.
[3] **ECG**: A 12-Leads ECG will be performed at every on-site study visit.
[4] **Blood pregnancy test:** Applicable to all women of childbearing potential at D0 and at EoS. In order not to limit the patient enrollment a urine pregnancy test can be performed in addition if the blood test result is not available at the time of randomization.
[5] **Hematology + Biochemistry:** samples to be taken at every on-site study visit (except D7 for outpatients if not possible) and analyzed locally.
[6] **CRP, Troponin I & T and D-Dimer:** samples to be taken at every on-site study visit (except D7 for outpatients if not possible) and sent to central laboratory for biobanking purpose.
[7] **Immunophenotyping and cells activation markers:** samples will be taken in all sites at D0, then only in selected sites and for hospitalized patients in French sites.
[8] **Blood sample Cytokines:** samples will be taken in all sites at D0, then only in selected sites and for hospitalized patients in French sites.
[9] **Chest CT-scan:** procedure concerns hospitalized patients only. Images taken at discharge will be assessed locally, then collected and sent to a blinded central reader for descriptive analysis of the lesions. If available at D0, Baseline CT scans of hospitalized patients will be sent to Central Reader for comparison purpose.
[10] **ABX464/placebo treatment dispensation**: treatment dispensation will be allowed once all the selection criteria are confirmed, including laboratory assessments for patients' eligibility confirmation.

5.2. Study conduct

It is the Investigator's responsibility to ensure that all the assessments are carried out during each visit and that the intervals between visits/follow-ups are adhered to.

5.2.1. Visit 1 – Day 0 (D0 / Baseline)

The patient will be informed about the general aspects of the study and will sign and date the informed consent form. Only when patient written informed consent has been collected may further study procedures be carried out.

The patient number will be allocated once the patient is created in the eCRF.

At baseline, the following assessments will be performed:

- All inclusion/exclusion criteria will be verified,
- Collection of the signed informed consent form,
- Demographic data collection: year of birth, gender and ethnicity,
- Medical history documentation including comorbidities or associated risks,
- Start date (Onset) of COVID-19 symptoms and contamination date if known,
- All current medications must be recorded and all changes must be documented during the course of the study,
- Complete physical examination,
- Vital signs, body weight and height measurement,
- Record a 12 leads ECG,
- Supply outpatients with oximeter, and explain purpose and how to use it
- Collect samples for
    - Analysis performed by local lab: Hematology, biochemistry, serum pregnancy test for women of child-bearing potential (- an additional urine pregnancy test can be done if the result of the serum test is not available at the time of the study drug dispensation)
    - Biobanking purposes:
        - Viral load testing (nasopharyngeal and blood),
        - CRP, Troponin I & T and D-dimer,
        - Cytokines testing,
        - Immunophenotyping and cells activation markers,
    - miRNA124 assessment (Blood PAXgene® tubes),
- Patient randomization,
- Dispensation of study treatment allocated to the patient once all the selection criteria have been confirmed (including laboratory assessments for patients' eligibility)
- Administration of the first intake on site for safety purpose; Instruct the patient how to take the study drug once at home.
- Record all adverse event (if any) starting from the informed consent signature,
- Schedule next on-site visit and/or remote medical monitoring.

5.2.2. Follow-up of out-patients between D0 and D14

After D0, outpatients will be contacted every other day by the investigator or his/her designee.

During this remote medical monitoring, outpatients will be questioned on their state of health, including body temperature, SPO2, clinical signs and occurrence of any potential adverse events as well as any change in the current medication will be checked. Data will be recorded in the patient's medical chart and in the dedicated page of the eCRF.

In case of any sign of worsening, outpatients will be asked to come back to the study site for an unscheduled visit where additional examinations will be performed.

During the last daily contact, the D14 onsite visit will be confirmed to the patient. Patients will be asked to bring back the oximeter provided at D0.

If no quarantine period is applied or if patients migration to the study site is acceptable as per local country regulation, outpatients will perform a D7 visit on-site where the same examinations as hospitalized patients will be done.

5.2.3. Visit 2 – Day 7 (+/- 2 days)

For Patients hospitalized at D7 (or since D7), the following assessments will be performed:

- Change in current medication will be checked and recorded,
- Complete physical examination and only changes from last visit will be recorded,
- Vital signs measurement,
- Record a 12-leads ECG,
- Collect samples for
    - Analysis performed by local lab: Hematology, biochemistry
    - Biobanking purposes:
        - Viral load testing (nasopharyngeal and blood),
        - CRP, Troponin I & T and D-dimer,
    - miRNA124 assessment (Blood PAXgene® tubes),
- Adverse Event and follow-up and reporting (if any).

NB: At any visit, for hospitalized patients: collect chest CT scan and send to central reader for analysis.

5.2.4. Visit 3 & 4 – Day 14 & 21 (+/- 2 days)

At D14 and D21, the following assessments will be performed:

- Change in current medication will be checked and recorded,
- Complete physical examination and only changes from last visit will be recorded,
- Vital signs measurement,
- Record a 12-leads ECG,
- Collect samples for
    - Analysis performed by local lab: Hematology, biochemistry
    - Biobanking purposes:
        - Viral load testing (nasopharyngeal and blood),
        - CRP, Troponin I & T and D-dimer,
        - *Only for France **at D14**: Cytokines testing, Immunophenotyping and cells activation markers,*
- Adverse Event and follow-up and reporting (if any),
- Schedule next visit and during D21 visit, instruct the patient to bring back the treatment kit for accountability purpose.

NB: At any visit, for hospitalized patients: collect chest CT scan and send to central reader for analysis

5.2.5. Visit 5 / End of Treatment visit (EoT) – Day 28 (+/- 2 days)

At Day 28, the following assessments will be performed:

- Change in current medication will be checked and recorded,
- Complete physical examination and only changes from last visit will be recorded,
- Vital signs measurement,
- Record a 12-leads ECG,
- Collect samples for
    - Analysis performed by local lab: Hematology, biochemistry,
    - Biobanking purposes:
        - Viral load testing (nasopharyngeal and blood),
        - CRP, Troponin I & T and D-dimer,

        - *Only France at D28: Cytokines testing, Immunophenotyping and cells activation markers* Cytokines testing,
        - Immunophenotyping and cells activation markers,
    - miRNA124 assessment (Blood PAXgene® tubes),
- Adverse Event and follow-up and reporting (if any),
- Collect the treatment kit dispensed at D0 for drug accountability and check patients' compliance,
- Schedule the End of Study visit.

NB: At any visit, for hospitalized patients: collect chest CT scan and send to central reader for analysis

5.2.6. Visit 6 / End of Study visit (EoS) – Day 49 (+/- 2 days)

Day 49 visit is the 6th and last study visit.

The following assessments will be performed:

- Change in current medication will be checked and recorded,
- Complete physical examination,
- Vital signs,
- Record a 12 leads ECG,
- Collect samples for
    - Analysis performed by local lab: Hematology, biochemistry, serum pregnancy test for all women of childbearing potential
    - Biobanking purposes:
        - CRP, Troponin I & T and D-dimer,
        - *Only France at D28: Cytokines testing, Immunophenotyping and cells activation markers*
- Adverse Event follow-up and reporting (if any).

5.2.7. Unscheduled visit

An on-site visit is defined as unscheduled if occurring between 2 on-site visits.

During such visit, the following examination will be performed:

Change in current medication will be checked and recorded,

- Complete physical examination,
- Vital signs,
- Record a 12 leads ECG,
- Collect samples for
    - Analysis performed by local lab: Hematology, biochemistry
    - Biobanking purposes:
        - CRP, Troponin I & T and D-dimer,
        - Cytokines testing,
        - Immunophenotyping and cells activation markers,

5.3. Detail of the study assessments

5.3.1. Physical Examination and Vital Signs

A routine physical examination, including body weight and vital signs measurements, will be done at each study visit. (except at D7 for outpatients due to quarantine measures). Physical examinations will cover eyes, ears, nose, throat, lungs/thorax, heart/cardiovascular system, abdomen, skin and mucosae, nervous system, lymph nodes, musculo-skeletal system, and, if applicable, others. Any new clinically relevant finding compared to baseline must be recorded in the dedicated section of the eCRF and documented as an adverse event (AE) when clinically significant in the investigator's judgment.

Measurements of vital signs will be done at each visit (blood pressure, heart rate, body temperature). The patient should rest for at least 5 minutes prior to measurements. The measurements can be performed either in sitting or

supine position of the patient. The right or left arm may be used. However, the position and the arm used for measurement should be kept constant throughout the trial for an individual patient.

The investigator should ensure that each parameter outside the normal range is assessed for clinical significance. For any excursion assessed clinically significant, the investigator must document the change as an adverse event in the eCRF dedicated pages.

In addition, it is at the discretion of the investigator to document any change or trend over time in vital signs as an AE if he/she considers the change to be clinically significant, even if the absolute value is within the alert limit or reference range.

5.3.2. Adverse Events of Interest

Treatment with ABX464 has been associated with the occurrence of mainly mild to moderate Adverse Events; more specifically with skin lesions. To collect information regarding this Adverse Event of Interest, the following procedure should be applied:

- In case of occurrence of a skin lesion (regardless of its severity), a dermatologist consultation should be scheduled to evaluate the type of lesion, its severity, etiology (i.e. consequence of SARS-CoV-2 infection or not) and relationship to the study treatment. An anonymized medical report shall be provided to the Sponsor.

5.3.3.Pregnancy

For all female patients of childbearing potential, a blood pregnancy test (beta human chorionic gonadotropin [β-HCG]) will be performed at baseline and at EoS. In case of positive pregnancy testing, detailed procedures can be found in section 8.3.3.

In addition, a urine pregnancy test can be performed at D0 provided that the β-HCG testing has been done but the result is not available at the time of the first ABX464 or matching placebo administration.

Should the partner of a male patient become pregnant, investigators will also collect pregnancy information while the patient is participating in this study. A specific informed consent will be collected from the pregnant partner to allow data collection.

5.3.4.ECG

Electrocardiograms will be performed at all study visits. A 12-lead ECG with recordings of at least 6 action potentials in lead II (paper speed 25mm/s, amplitude 10mm/mV) will be measured in a resting position. Prior to the recording the patient should be at rest for five minutes minimum. Resting ECG should be performed before any examinations.

The ECG printout will be reviewed by the Investigator, then signed, dated and attached to the medical file. Original ECG printouts are considered as source data and should be stored at site. If thermal paper is used, a copy of the original ECG must also be kept.

All abnormal findings must be documented in the e-CRF. Any clinically relevant findings compared to ECG done at Day 0 must be documented as adverse events.

5.3.5.Chest CT-Scans

During the course of the study, should a patient be hospitalized as a consequence of Covid-19 infection, a chest CT scan will be obtained and sent to a blinded Central Reader provider for assessment. If a CT scan was done at D0 as per site standard of care, the baseline CT scan will be collected and sent to the Central Reader for comparison purpose. Presence or absence of infiltrates or lesions will be described in the analysis.

5.3.6.Laboratory parameters

Parameters will be assessed either by the site local laboratory (for routine analysis) or a central laboratory (for specific analysis).

Each laboratory value that is outside of the institution's normal range will be identified. The Investigator will be responsible for assessing the clinical significance of laboratory abnormalities. If the Investigator is uncertain about the clinical significance of a laboratory abnormality, he/she will consult with the Sponsor medical monitor.

The Investigator should follow any clinically significant laboratory abnormalities until resolution.

Table 2 lists all the clinical laboratory parameters that must be measured and the central laboratory in charge of their analysis.

Table 2: Laboratory Tests

LABORATORY	ANALYSIS	PARAMETERS
Local lab	HEMATOLOGY	Hemoglobin, Hematocrit, WBC (Absolute & differential), Platelet Count Prothrombin time or INR
	BIOCHEMISTRY	Sodium, Potassium, Chloride, Calcium, Phosphate, Glucose, BUN or urea, Creatinine, AST / ALT, Lipase, Alkaline phosphatase, gGT, Total bilirubin, Total protein, Albumin, LDH, CRP, β-hCG, Fibrinogen,
Hematology Department of H.E.G.P.	BIOBANKING	Immunophenotyping: CD11b, CD15+, CD24+, CD114+, CD182+, CD66b, CD3; CD4; CD8; CD19; CD16/CD56, CD161, CCR6, IL-23R but not limited to Cytokines assessment: MCP-1, MIP-1 α, G-CSF, IL-1b, IL-2, IL-6, IL-7, IL-10, IL-17, INFg, IP-10, RORγt and TNFa but not limited to.
Hematology Department of H.E.G.P.	BIOBANKING	Troponin I & T, CRP, and D-dimer
Hematology Department of H.E.G.P.	viral load determination	SARS-CoV-2 quantitative PCR
Acobiom	Micro RNA 124	miR-124

5.3.6.1. miRNA-124 modulation

ABX464 up-regulates miRNA-124 in PBMCs, making of this micro-RNA a potentially useful biomarker for ABX464 treatment monitoring. Determination of miRNA-124 level in total blood will be performed in order to assess treatment effect by comparing before and after treatment. Assays for miRNA-124 determination will be conducted at the end of the study.

5.3.6.2. Viral load assessment

Viral load will be assessed by a central laboratory at each on-site study visit from D0 to D28 by qPCR performed on nasopharyngeal and blood samples.

5.3.6.3. Lymphocyte Phenotyping, Cytokine Serum Concentrations

Blood and serum samples will be collected at D0 in every site, and then at specified timepoints during the study in French sites only and for hospitalized patients, to document effects of ABX464 on T cell, NK and dendritic cell concentrations as well as on cytokines (as described in table 1: Laboratory tests). These determinations will be performed by a central laboratory.

5.3.6.4. Volume of blood sampling

The table 3 below summarizes the volume of blood to be sampled at each study visit. The total (maximal) volume of blood taken from a participating patient is 260 mL to 328 mL (including samples taken during an unscheduled visit).

Table 3: Blood Volume

	REQUIRED VOLUME	COLLECTION TUBE	D0	D7	D14	D21	D28/EOT	UNSCH	D49/EOS
Hematology	0,5 mL - EDTA Blood	2 mL EDTA Tube	2	2	2	2	2	2	2
Biochemistry	2 mL - serum	2x 5mL serum gel tube	10	10	10	10	10	10	10
Pregnancy test	*included in biochemistry panel*	*n/a*	*X*	'-	'-	'-	'-	-	*X*
Immunophenotyping	24 ml of blood	3 x 8 mL CPT tube	24		24		24	24	
Biobank	21 - mL Serum	2 x 3.5 mL dry tube 2 x 3.5 mL EDTA tube 3 x 3.5 mL Citrated tube 1x 5mL serum gel tube	29,5		29,5		29,5	29,5	
miRNA-124 & viral load (Blood PAXgene tube)	5mL - Blood	2 x 2,5 mL PAXgene® tube	5	5	-	-	5	-	-
Viral load	2,5 mL - Blood	1 x 2,5 mL PAXgene® tube	2,5	2,5	2,5	2,5	2,5	2,5	
TOTAL PER VISIT			73	19,5	68	14,5	73	68	12

6. INVESTIGATIONAL PRODUCT(S)

All investigational products to be used in this study have been manufactured, packaged and labelled by contract manufacturers for ABIVAX, according to GMP standards and are supplied to investigators free of charge.

6.1. Description of investigational treatment

The study treatment that will be administrated to patients enrolled in this Phase 2/3 study consists of capsules containing ABX464 or its matching placebo given orally once daily with food for 28 days.

6.2. Description of investigational Product

6.2.1. Active investigational product (ABX464)

The ABX464 investigational medicinal product (IMP) is a hard gelatin capsule intended for oral administration.

For the proposed clinical trial, the IMP consists of size 01 capsules containing 50mg of ABX464 drug substance in the form of granulate prepared with several common excipients (microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate and colloidal silica).

It is supplied in study specific high-density polyethylene bottles.

ABX464 will be manufactured by:

DELPHARM Lille SAS
Parc d'activité Roubaix Est
22, rue de Toufflers
CS 50070
59 452 Lys-Lez-Lannoy France

Packaging and labelling activities, as well as Qualified Person release of the IMP will be performed at the following site:

Creapharm Clinical Supplies
Z.A. Air Space
Avenue de Magudas CS 2007
33187 Le Haillan Cedex France

Storage conditions: Do not store above 30°C (86°F). Do not refrigerate or freeze.

6.2.2. Placebo

The matching placebo consists of the same hard gelatin, powder-filled capsules (size 01) filled with only the same common excipients (microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate and colloidal silica) as the active IMP. It is supplied in high-density polyethylene bottles closed with child-resistant polypropylene screw caps with induction seals.

ABX464 matching placebo will be manufactured by:

DELPHARM Lille SAS
Parc d'activité Roubaix Est
CS 50070
59 452 Lys-Lez-Lannoy France

Packaging and labelling activities, as well as Qualified Person release of the IMP will be performed at the following site:

Creapharm Clinical Supplies
Z.A. Air Space
Avenue de Magudas CS 2007
33187 Le Haillan Cedex

Storage conditions: Do not store above 30°C (86°F). Do not refrigerate or freeze.

6.3. Administration and dosing

6.3.1. Administration of the investigational product

Depending on the randomization, patients will be treated with a daily dose of 50mg of ABX464 or its matching placebo. All patients regardless of the treatment group will receive 1 capsule every day.

Patients will be orally dosed in a fed condition (regular breakfast) with a glass of water. In case the patient is intubated, it's allowed to administer the study treatment through the feeding tube.

Should a patient be hospitalized during the course of the study, every effort should be made to ensure treatment compliance.

6.3.2. Guidelines for treatment postponement and dose modifications

No dose escalation/dose adjustments are allowed.

6.4. Method of assigning patients to treatment arms

All patients will be assigned a unique and incremental Patient Identification (ID) number. Patient IDs will be unique (i.e. reallocation of the ID will not be permitted). The format will be a seven-digit number as follows: site number (4 digits) – Patient number (3 digits). The latter 3-digit Patient number will be assigned according to the patient's order of inclusion in the center.

Eligible patients (i.e. those who fulfil all inclusion/exclusion criteria) will be randomized across the study according to a 2:1 ratio to ABX464 50mg : placebo treatment arms.

Randomization will be performed via IWRS. Treatment numbers will be allocated as per randomization list.

In all cases at the end of treatment visit, all patient should return the bottle dispensed at D0 for a compliance check.

6.5. Blinding and breaking the study blind

Study drug will be packaged in blinded high-density polyethylene bottles. Bottles will be numbered according to a randomized treatment number list. The content of the labeling is in accordance with the required references listed in the Good Manufacturing Practices.

The investigator, study personnel, and study participants are blinded with respect to treatment (i.e., active ABX464 or placebo). Sponsor or delegate will generate the random code list and the corresponding treatment number list.

Investigators may have access to unblinding only in case of medical emergency. The code breaks will be available 24 hours a day and 7 days a week using an Interactive Web Response System (IWRS).

The IWRS will require an access code/password/PIN and is only available to staff members delegated by the PI and named on the delegation log of each site.

The investigators and delegated members with unblinding responsibilities are responsible for testing their username and password prior to the treatment of patients to ensure unblinding is possible, or for ensuring appropriately trained staff members are available to action code breaks when required for medical emergencies which may be required out of normal working hours.

Details of any emergency unblinding shall be documented fully in the TMF and Investigator/Pharmacy Site File. The sponsor should be notified of the unblinding and be provided with the patient number but NOT the result. The details shall be included in the statistical report.

However, as there is no antidote, it is highly unlikely that knowledge of treatment would affect the clinical management of the patient. In case of unblinding, the patient will be immediately withdrawn from the study.

6.6. Packaging

The IMP consists in hard gelatin, powder-filled capsules (size 01) containing 50 mg of ABX464 supplied in study specific high-density polyethylene bottles.

6.7. Storage

ABX464/Placebo capsules will be shipped to the investigational site at a temperature not above 30°C (86°F).

Storage conditions: do not store above 30°C (86°F).

The IMP should not be used beyond the expiration date. Drug supplies are to be stored in a secure, limited-access location under the storage conditions required by GCP/GMP guidelines.

6.8. Product Accountability

An accurate and current accounting of the dispensing and return of IMP(s) will be maintained on an ongoing basis by the pharmacist and a member of the study site staff in the Accountability Log and case report form and will be verified by the study's monitor.

6.9. Prior and Concomitant Medication

6.9.1. Allowed concomitant treatment

Are allowed all medications related to patient's current affection (i.e. medical history).

6.9.2. Prohibited concurrent medications

The following drugs are prohibited at enrollment and during the study:

- all immunosuppressor or immunomodulator agents (cf. appendix #2)
- Use of any investigational or non-registered product within 3 months or within 5 half-lives before enrollment, whichever is longer.

The following drugs are prohibited during the study:

- Drugs that could interact with ABX464 should be avoided especially the CYP1A2 substrates (cf. Appendix #1). The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (clozapine, theophylline, ropinirol, warfarin and methadone). In case of concomitant treatment with ondansetron the maximal daily dose must be limited to 8 mg.
- Inhibitors or inducers of the CYP1A2 (cf. Appendix #1).

7. STUDY COMPLETION

7.1. Patient Completion

Treatment with ABX464/Placebo shall continue until D28 included, except if a patient fulfils a premature discontinuation criterion (defined below). After D28, patients will come back 21 days later to perform the End of Study (EoS) visit.

After EoS visit, patients will exit the study and will be treated/follow-up according to the site standard of care.

7.2. Patient Premature trial discontinuation

A patient can be withdrawn at any time from the study. Premature trial discontinuation could occur for the following reasons:

- Investigator's decision.
- An Adverse Event or an intercurrent condition that preclude continuation of treatment.
- Specifically, an elevation ≥ 3.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or Alkaline phosphatase or in total bilirubin compared to baseline requires close observation with repeating liver enzymes and serum bilirubin tests every 2 days. Discontinuation of the study treatment should occur if:
    - ALT or AST > 8xULN
    - ALT or AST > 4xULN and total bilirubin > 2xULN or INR>1.5
    - ALT or AST > 4xULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Any relevant toxicity or negative change in the risk/benefit assessment leading to an unacceptable risk for the patient (i.e. occurrence of adverse events which character, severity or frequency is new in comparison to the existing risk profile), or any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment.
- Major protocol violation.
- Withdrawal of consent.
- Administrative reasons from Sponsor.

A patient who prematurely exits the study will not be replaced.

All patients, regardless of the completion or premature discontinuation, should perform the End of Study Visit 21 days after the last study drug intake, according to the study flow-chart.

7.3. Baseline Failures

A patient who does not fulfil the randomization criteria will be considered as baseline failure. All patient data should be entered in the eCRF including the failure data. Based on the investigator evaluation and sponsor prior approval, a non-randomized patient case can be re-evaluated for randomization. This re-procedure should be documented, the patient should consent again and a new unique and incremental patient Identification (ID) number be allocated.

All potential patients who are assessed for enrolment in this study will be listed on the patient Log/Identification List. Reasons for exclusion will be recorded for potential patients who do not enter the study.

7.4. Study Discontinuation

The 50 mg QD dose is well tolerated. Some patients are being treated for more than 2 years at that dose. No DLT has been reported. The study protocol plans some early discontinuation criteria and specifically in case of modification of LFTs in accordance to the pre-clinical findings.

In addition, all safety data will be thoroughly reviewed by the DSMB. Part of the DSMB duties is to review occurrence of adverse events which character, severity or frequency is new in comparison to the existing risk profile. In such case, recommendations from the DSMB may lead the either additional stopping rules up to study discontinuation.

7.5. End of Trial

In the frame of the abx464-401 study, the end of trial will occur once the last randomized patient has performed the end of study visit. Then all data will be analyzed and embed in a clinical study report.

8. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE. During the study, in case of a safety evaluation, the investigator or site staff will be responsible for reporting AEs and SAEs, as detailed in this section of the protocol.

All Serious AEs will be collected from the time of signing of ICF through to 4 weeks post end of treatment visits.

Any disease progression will be both reported in the eCRF as an adverse event and documented in the efficacy section.

8.1. Definitions

8.1.1. Definition of an Adverse Event (AE)

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

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

Note: The official definition also extends to AEs occurring in the placebo arm. Because of regulatory requirements, events occurring during pre-and post-treatment periods will also be designated as AEs. Therefore, reporting of such events, AEs and SAEs, will start when the patient is enrolled into the study (date of signature of the informed consent) up until 4 Weeks after the end of the treatment visits. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

8.1.2. Definition of an Adverse Drug Reactions (ADR)

A response to a medicinal product which is noxious and unintended.

Suggesting that there is at least a reasonable possibility or suspicion of a causal relationship between the medicinal product and an adverse event.

8.1.3. Definition of a Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

A serious adverse event (experience) or reaction is any untoward medical occurrence that, at any dose:

a) Results in death

NOTE: Death is an outcome of an AE, and not an AE in itself. Event which led to death should be recorded with fatal outcome.

b) Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization means that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

Hospitalization for Covid-19 infection consequences will not be reported as a Serious Adverse Event.

Hospitalization for elective treatment of a pre-existing condition that did not worsen after informed consent was given is not considered serious.

d) Results in persistent or significant disability/incapacity,

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated

headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Is another medically important condition: This refers to an AE that may not be immediately life-threatening or results in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Based on medical and scientific judgment this should usually be considered serious.

If there is any doubt about whether or not an AE is serious, the investigator should contact the sponsor.

8.1.4. Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR), is a serious adverse reaction (SAR) for which a reasonable causal relationship with the medicine use is suspected but not confirmed. Unexpected in this context means not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

8.2. Events and/or Outcomes Not Qualifying as SAEs

Any hospitalization, or prolongation of hospitalization due to the circumstances listed below, will not be reported as SAE:

- planned medical/surgical procedure;
- planned medical/surgical admission (planned prior to entry into study, appropriate documentation required), for the disease under study;
- Administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances).

8.3. Events or Outcomes Qualifying as AEs or SAEs

8.3.1. COVID-19 related AE/SAEs

All COVID-19 related AE/SAEs will be recorded.

8.3.2. Clinical laboratory parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g. vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definitions of section 8.1. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at informed consent and significantly worsen during the study will be reported as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied and are present at the start of the study will be recorded as medical history and will be reported as AEs or SAEs in case of worsening.

8.3.3. Pregnancy report

Patients who become pregnant at any time will be immediately withdrawn from participation in the study. All appropriate withdrawal assessments may be performed at the discretion of the investigator.

The investigator will collect pregnancy information on any woman patient or partner of a male patient, who becomes pregnant and their partner while participating in this study. The investigator will record pregnancy information on a specific pregnancy notification form and submit it to ABIVAX or its designee within 24 hours after knowledge of a patient's or partner's pregnancy. The patient or partner will also be followed to determine the outcome of the pregnancy, be it full-term or prematurely terminated. Information on the status of the mother and child will be forwarded to ABIVAX or its designee. Follow-up will end 6 to 8 weeks following the estimated delivery date.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

The time period for collecting pregnancy information is identical to the time period for collecting AEs, as stated in Section 8.4, Time Period, Frequency, and Method of Detecting AEs and SAEs. Pregnancy information is collected from the signing of informed consent to 4 Weeks after the last dose.

8.4. Expected adverse events from previous clinical trials

More than 300 patients have already received ABX464 at different dose levels and for different durations. ABX464 is generally well-tolerated. The most frequently reported side effects with ABX464 treatment are:

- Occuring in more than 10% of the patients: headache, nausea, vomiting, gastrointestinal tract disorders (upper abdominal pain).

All these adverse reactions were either mild or moderate and only 2 led to treatment stop. The frequency of these adverse events seemed to be dose-related, starting from 75mg and higher.

- Ocurring in less than 10% of the patients: Diarrhea, Fatigue, Edema, Muscle and joint pain, Dizziness, Fever, Skin rash, Pruritus, Conjunctivitis.

8.5. Time Period, and Frequency of Detecting AEs and SAEs

All AEs and SAEs occurring from the time a patient consents to participate in the study until 4 Weeks after he or she has completed or discontinued the investigational product must be recorded in the Patient's eCRF.

Moreover, any occurrence of pregnancy within 6 months post stopping dosing must be reported.

Importantly, SAEs will have to be reported, **either by email or by Fax, to IntuVigilance Limited within 24 hours of awareness of an SAE**.

IntuVigilance Limited

UK:
Scotsbridge House, Scots Hill
Rickmansworth WD3 3BB
Hertfordshire, UK

Hotline phone: +44 800 689 4129

Email Address: safety@intuvigilance.com

Fax number: +44 800 915 6753

Legislative guidance requires the investigator to also ensure that any **related** SAEs are reported after the patient finished the study if the investigator becomes aware of them.

8.6. Recording AEs and SAEs

Severity of AEs will be assessed according to CTC-AE Classification Version 5.0.

Patients will be asked to report all AEs as part of the procedures performed at each study visit. The site personnel will document all AEs in the patient's medical record. All AEs subsequently must be recorded in the appropriate eCRF sections.

The following points must be recorded for each event:

- A description of the event in medical terms, not as reported by the patient,
- Date of onset (start date),
- Date of resolution (stop date),
- The time of onset with respect to administering the investigational product,
- The severity of the sign/symptom or clinically significant abnormal laboratory value according to CTC-AE Classification (Most recent version),
- The causal relationship between the investigational product and the occurrence of each AE. This will be assessed by each investigator using clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant medications, other risk factors and the temporal relationship of the event to the investigational product will have to be considered. The causality of all AEs should be assessed by the

investigator with the following question: Is there a reasonable possibility that the AE may have been caused by the investigational product? And answered "NO" (if not related) and "YES" (if related);

- Action taken regarding the investigational product:
  - No action;
  - Temporary discontinuation;
  - Permanent discontinuation;
  - Patient's outcome:
  - Recovered without sequelae / resolved without sequelae;
  - Recovered with sequelae / resolved with sequelae;
  - Recovering/Resolving;
  - On-going;
  - Fatal (for SAEs only).

If in any one patient, the same AE occurs on several occasions, the AE in question must be documented and assessed anew each time.

8.7. Reporting of SAEs to ABIVAX or its designee

Throughout the study, the reporting of SAEs to the Sponsor or its designee will be done through the SAE forms.

It is the investigator's responsibility to ensure that the SAE report is submitted to IntuVigilance Limited **within 24 hours after knowledge of the event(s).**

The study specific SAE form should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. The investigator will assess causality between the study drug and the adverse event (AE) / serious adverse event (SAE) according to the table outlined below:

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 to be 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).

An assessment of causality should always be provided at the time of the initial report. If the investigator or designee does not have all information regarding the SAE, he/she should not wait to receive additional information before completing the form and notifying IntuVigilance Limited.

Additional or follow-up information relating to the initial SAE report, will be requested, if necessary. Again, this information is to be completed and submitted through the SAE forms within 24 hours of receipt of the information.

In the rare occasion when the facsimile equipment does not work and in the absence of, the investigator should notify IntuVigilance Limited by telephone within the given timeframe and send a copy of the SAE report form by email.

8.8. Reporting of SAEs to Regulatory Authorities

ABIVAX has a legal responsibility to notify, as appropriate, both the local regulatory authorities and other regulatory agencies about the safety of the investigational medicinal product. It is therefore important that the investigator notifies promptly (within 24 hours) ABIVAX or designee of any SAEs, in order for legal obligations and ethical responsibilities towards other patients to be met.

In addition, the investigator or designee, will comply with the local regulatory requirements (when applicable) in reporting of SAEs to the ethics committee and, if required, to the relevant government authority.

Safety reports on adverse events that are serious AND unexpected AND causally associated with the investigational product are prepared according to ABIVAX's policy and applicable regulations and are forwarded to the investigators. These reports are filed with the investigator brochure or other appropriate study documentation. It is the Sponsor or its designee and/or investigator's responsibility to notify the IRB or IEC of these reports, if applicable according to local requirements.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

A summary of the principal features of the statistical analysis of the data will be described here, in the statistical section of the protocol. A more technical and detailed elaboration of the principal features stated in the protocol will be given in the first version of the statistical analysis plan (SAP).

Any amendments to the SAP will be clearly documented and signed prior to the final database lock including justifications and details of their potential impact on the interpretation of the study results.

9.1. Statistical and Analytical Plans

9.1.1. Protocol deviations

Protocol deviations will be reviewed and classed as major or minor during the blind-review meeting. Major protocol deviations are defined as deviations liable to bias the evaluation of the main efficacy endpoint. The following deviations will be considered as major (non-exhaustive list):

- Non compliance with the inclusion or exclusion criteria;
- Non compliance with the study treatment;
- Intake of prohibited medication;
- Noncompliance with time window.

9.1.2. Definition of study analysis sets

The following datasets will be defined and used for the analyses:

- The Safety dataset (SAF population) is defined as those patients included in the study, who have received at least one dose of the study treatment.
- The Full Analysis dataset (FAS population) is defined as those patients included in the study, who have received at least one dose of the study treatment, and who have at least one baseline data.
- The Per Protocol dataset (PP population) is defined as those patients of the FAS population without any major protocol deviation.

9.1.3. Patients/Patients disposition

The number and the percentages of patients enrolled and included in each of the populations will be tabulated. The reason for patient exclusions from each of the populations will also be listed. In addition, the number of discontinued patients with their reason for discontinuation will be tabulated.

9.1.4. Demographic and other baseline characteristics

Demographics and other baseline characteristics will be summarized by treatment arm. This analysis will be conducted on the FAS population.

9.1.5. Treatment compliance

Number of daily doses will be presented on the FAS population.

9.2. Safety Analyses

Adverse events will be coded using the standard dictionary (MedDRA) down to the lower level term (LLT).

An overall summary table will be presented (Any adverse event, any treatment emergent adverse event (TEAE), any serious adverse event (SAE), death, any grade 3 or higher adverse events from baseline to the end of Study. This analysis will be conducted on SAF population.

Two periods will be defined for TEAE:

- Any adverse event which occurs or worsens from first dosing to Day 28;
- Any adverse event which occurs after Day 28.

Adverse events will be described by primary system organ class and preferred term. Numbers and percentage of patients, and number of occurrences of adverse event will be presented for:

- TEAE;
- Serious TEAE;
- TEAE leading to drug discontinuation;
- TEAE of grade 3 or 4;
- TEAE for which relationship with the study drug is recorded as possible or probable.

The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the CTC-AE Classification (version 5.0) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and PCSAs [potentially clinically significant abnormalities (PCSAs) determined upon investigator considerations].

Adverse events will be tabulated (counts and percentages) by group. All adverse events will be listed, and the data will be tabulated by body system/organ class. Adverse event tabulations will include all treatment emergent adverse events, which will be further classified by severity, and relationship to treatment and dose level.

Clinical laboratory parameters, vital signs, ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Number of patients with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables, by group and dose.

9.3. Efficacy Analysis

9.3.1. Generalities

All efficacy analysis will be conducted on both FAS and PP population except if otherwise specified.

9.3.2. Analysis of Primary Efficacy Endpoint

Primary efficacy endpoint, number and rate of patient who do not require use of high-flow oxygen (use of high-flow oxygen being defined as settings of 3 L/min or greater AND with at least one SpO2 measurement < 92%, with or without O2 supplementation) or non-invasive mechanical ventilation (IMV and NIV, respectively) within 28 days and who are alive at the end of the 28 days period will be analyzed by likelihood ratio chi-square test on a two-sided 5% level.

9.3.3. Analysis of Secondary Efficacy Endpoints

Descriptive statistics will be presented by treatment arm for all secondary efficacy variables for each measurement timepoint.

Continuous variables: mean, standard deviation, minimum and maximum, two-sided 95% confidence intervals, median and quartiles will be presented when considered relevant.

Categorical variables: Counts, rates and two-sided 95% confidence intervals will be calculated.

Time-to-event variables will be analyzed by Kaplan-Meier plots.

Mixed model analysis of covariance will be conducted on changes from baseline in specifically chosen measurements defined in the SAP. In this model, treatments will be fixed effect, patients will be random effect and baseline values of the respective measurements will be covariates. Other explanatory variables will also be allowed to be included in the model. In order to normalize eventual skewed distributions transformation of the data will also be considered. Study groups will be compared within this model framework. All p-values in all analysis will be interpreted in a descriptive manner.

9.4. Clinical laboratory evaluation

Descriptive statistics for laboratory parameters will be computed at each scheduled assessment. If relevant for some parameter, descriptive statistics of change from baseline will also be presented.

In addition, shift tables from baseline will also be presented.

9.5. Determination of Sample Size

The primary efficacy endpoint is the rate of patients who do not require use of high-flow oxygen (use of high-flow oxygen being defined as settings of 3 L/min or greater AND with at least one SpO2 measurement < 92%, with or without O2 supplementation) or non-invasive mechanical ventilation (IMV and NIV, respectively) within 28 days and who are alive at the end of the 28 days period.

The primary endpoint will be compared between patients who received {Standard of care + ABX464} and {Standard of care + placebo}.

For the sample size calculation, the following assumptions will be made:

- Response rate (ABX464): 83 %
- Response rate (placebo): 75 %
- Type 1 error: 5% two-sided. Power: 80%
- 2:1 (ABX464 50mg: placebo) study treatment allocation ratio.

If the above assumptions hold true, then a total sample size of 897 patients will be required to be randomized (598 in the AX464 treatment group and 299 in the placebo group). It is assumed that 15% of patients will drop out prior to D28; leading to a total sample size of 1034 patients (690/344).

10. STUDY CONDUCT CONSIDERATION

10.1. Regulatory and Ethical Considerations

10.1.1. General Requirements

The study will be conducted in compliance with the study protocol, ABIVAX / CRO Standard Operating Procedures and in accordance with any local regulatory requirements, to ensure adherence to Good Clinical Practice (GCP) as described in the following documents:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6 (R2)).
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Directive 2005/28/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical studies on medicinal products for human use and its guidance.
- Declaration of Helsinki and its amendments.
- EudraLex GMP guidelines Annex 13 related to shipment, storage and handling of investigational products.

Upon signing the protocol, the investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

Written informed consents will be obtained for each patient before he or she can participate in the study.

ABIVAX will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agencies in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

10.1.2. Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the study protocol and amendments if applicable as well as other appropriate study-related documents will be submitted to an independent Institutional Review Board (IRB) or independent Ethics Committee (IEC), respectively.

For each center it will be individually specified, who (investigator or sponsor) will be responsible for informing the IRB or IEC, respectively of any protocol amendments or new relevant information that require an ethical reconsideration of the study protocol.

If the investigator is responsible for obtaining approval, he/she should also obtain a statement from the IRB or IEC, respectively that it is organized and operates according to GCP and applicable laws and regulations.

10.1.3. Patient Informed Consent

It is the responsibility of the investigator to give each patient full and adequate verbal and written information regarding the aims, methods, anticipated benefits and potential hazards. The patient must be informed that participation is voluntary, and that they are free to withdraw from the study at any time without any disadvantages for their subsequent care. Although a patient is not obliged to give her/his reason(s) for withdrawing prematurely from the trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Written consent (signed and dated by the patient and the investigator) must be obtained prior to admission. The patient must be provided with a copy of the patient information and informed consent.

The data collected in this study will be processed anonymously at ABIVAX. Patients should be informed about the purpose of the planned computer data processing and the publication of the data (e.g. at scientific meetings). The patient must give consent to the computer processing and to the publishing of anonymous data. The patient must be also informed of his rights related to the processing of his personal data and must acknowledge that.

The patient must be informed of and consent in writing that personal data relating to the trial may be subject to audits by Health Authorities and the sponsor. However, personal data will be kept strictly confidential and will not be made publicly available.

10.1.4. Compensation to Patients

Insurance coverage will be provided for all patients enrolled in the study from the time of the patient's inclusion in the study (i.e. date of signing the ICF). The insurance coverage will be provided by the Sponsor and will be in line with GCP guidance and legal requirements, but also in accordance with local regulations. A confirmation of insurance and corresponding insurance conditions should be archived in the Investigator File.

Besides, due to the cumbersome procedures related to the study (number of visits, imaging, pharmacokinetics samplings…) patients could be financially compensated by the Sponsor in accordance with the national regulations and the approval of the Ethics Committees.

11. STUDY MANAGEMENT

11.1. Remote Data Entry

An electronic case report form (eCRF) will be used to record all data required by the protocol. Remote Data Entry (RDE) will be used for data collection, *i.e.* the Patient's information pertaining to the study, will be entered into the eCRF via a computer at the investigational site.

Prior to the start of the study, the investigator will complete an "*Investigator site staff signature and task delegation log*" form, showing the signatures and initials of any person who is authorized to make or change entries in the eCRF and any person authorized to electronically sign the eCRF.

The eCRF used for this study is validated and fulfils the GCP ICH E6 (R2) requirements, European and FDA (21 CFR Part 11) regulations.

Training sessions will be held for all the participants who will use this tool (*e.g.* investigators, ABIVAX staff and contract research organization [CRO] staff, including project managers, CRAs and data managers).

Several supports are available to help all users with this tool including eCRF User Guide and five days a Week / working hours helpdesk (support line).

All of the information will be recorded through transcription from source documents into the eCRF by an authorized person.

The investigator is responsible for the management and accuracy of the information in the eCRF. At each monitoring visit, the patient medical files should be at the clinical research associate's (CRA) disposal for review.

11.2. Data management

Data management will be outsourced to a Contract Research Organization (CRO). The data managers will issue electronic edit checks via EDC, and modification of the data will be permitted by the investigator to achieve accuracy with source documents and eliminate all inconsistencies in the data.

The data will be reviewed for completeness and logical consistency. Automated validation programs will identify missing data, out of range data and other data inconsistencies at the time of entry.

All new/updated information will be reviewed and verified by the appointed monitor.

11.3. Data coding

Adverse events, concomitant diseases, medical/surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using the WHO-DRUG dictionary.

11.4. Randomization

Randomization will be centrally managed. It will be performed via the eCRF. The bottle numbers to be used for a specific patient will be assigned according to a pre-defined randomization list by the vendor in charge of drug supplies. This information will be provided to the site by fax or by email.

11.5. Study Monitoring

The study will be conducted in accordance with the related topic of the ICH E6 (R2) GCP guidelines. The appointed monitor will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ABIVAX requirements. Throughout the study, the monitor will arrange visits to the study center at appropriate intervals to assess the progress of the study and review the completed eCRFs.

During the monitoring visits, the monitor will:

- Ensure that the safety and the rights of patients are being protected;
- Check that the data are authentic, accurate, and complete and discuss any inconsistencies;
- Ensure that all study materials are correctly stored and dispensed with particular emphasis to the investigational product;
- Verify that the site staff and facilities continue to be adequate for the proper conduct of the study;

- Ensure that the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements;
- Help resolve any problems that may have arisen.

In line with the ICH E6 (R2) GCP guidelines, monitoring will include verification of data entered in the CRF against the original patient records. Therefore, for the purpose of monitoring review, direct access to all study-related site and source documents is mandatory. Data items for which the eCRF will serve as the source document will be identified, agreed upon and documented. The investigator must also ensure provision of sufficient time, space and qualified personnel for the monitoring visits.

During the Covid-19 outbreak, on-site monitoring visits might be postponed and delayed due to national contingency measures. Remote monitoring will be preferred during this period.

11.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff.

ABIVAX will inform the investigator/institution of the required time period for retaining these records in order to be compliant with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study site, as dictated by ICH E6 (R2) section 4.9, any institutional requirements or local laws and regulations, or ABIVAX standards/procedures; otherwise, by default the retention period will be 15 years.

The investigator must notify ABIVAX of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site. In addition, the investigator should seek the written approval of the Sponsor prior to disposing any of the archived records.

11.7. Quality Assurance and Inspection by Authorities

To ensure compliance with GCP and all applicable regulatory requirements, ABIVAX may conduct quality assurance audits. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. By signing the protocol agreement page, the investigator agrees to permit drug regulatory agencies and ABIVAX audits. If an audit or inspection occurs, the investigator and institution will allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. Items of particular interest in case of an audit are, but not limited to, the following:

- IRB/IEC and regulatory authority approvals;
- Informed consent forms of the patients;
- Approved study protocol and amendments and investigator brochure;
- Treatment accountability;
- Safety reporting;
- Study file;
- Study personnel;
- Log of monitoring visits and monitoring process;
- Medical records and other source documents;
- Site facilities;
- Reports to the IRB/IEC and the sponsor;
- Record retention.

11.8. Study and Site Closure

If the study is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients

ABIVAX reserves the right to temporarily suspend or prematurely discontinue this study, at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If such action is required, the Sponsor will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action, at that time. Advance notification will be provided to the site(s) when feasible, on the impending action prior to it taking effect.

All investigators and/or medical institutions conducting the study will be informed in writing should the Sponsor decide to suspend or prematurely discontinue the study for safety reasons. The regulatory authorities will also be informed of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by local regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

Upon premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and ABIVAX procedures. All data must be returned to ABIVAX. Arrangements will be made for any unused investigational product based on the relevant ABIVAX procedures for the study.

11.9. Study report and Publication

Upon conclusion of the study, an integrated clinical and statistical study report will be written by the Sponsor in consultation with the Coordinating Investigator. This report will be based on the items detailed in this study protocol. When the clinical study report is completed, ABIVAX will provide the investigators with a full summary of the study results. The investigators are encouraged to share the summary results with the patients, as appropriate.

The first resulting publication will be a full publication of all data from all participating sites, coordinated by ABIVAX. Any secondary publications by the investigators (abstracts in journals, oral presentations etc.) will reference the original publication and will require pre-submission review by the Sponsor. Note that the Sponsor is entitled to delay any proposed secondary publication, in order to obtain patent protection, if required.

The Coordinating Investigator as well as other members of the study committee will be authors on the first publication. The principal investigator of the trial will be the first author. Authorship for other investigators will be assigned on the basis of their recruitment contribution, as well as intellectual and administrative input. Ranking will be according to the number of patients randomized as well as contribution to the study conduct and preparation of final manuscript.

11.10. Ownership and Confidentiality

All information provided by ABIVAX and all data and information generated by the sites, as parts of the study (excluding the patients' medical records) are property of ABIVAX.

All potential investigators must be aware of and agree in writing (confidentiality agreement) to the confidential nature of the information pertaining to this study. Furthermore, all information provided by ABIVAX and all data and information generated by the sites during the study must be kept confidential by the investigator and other site staff and may not be used for any purpose other than conducting this study.

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13. APPENDICES

13.1. APPENDIX 1: CYPIA2 SUBSTRATES

CYPIA2 substrates/inhibitors/inducers (in bold: prohibited concomitant medications)

Substrates:

Alosetron, Duloxetine, Ramelteon, Tasimelteon, Amitriptyline, Clomipramine, Imipramine, Agomelatine, **Clozapine**, Olanzapine, Haloperidol, Ropivacaine, **Theophylline,** Zolmitriptan, Tamoxifen, Erlotinib, Cyclobenzaprine, Mexiletine, Naproxen, Ondansetron, Phenacetin, Paracetamol, Propranolol, Tacrine, **Tizanidine**, Verapamil, **Warfarin**, Zileuton, **Ropinirole, Methadone.**

Inhibitors:

Artemisinin, Atazanavir, **Ciprofloxacin, Enoxacin**, Ethinyl Estradiol, **Fluvoxamine,** Mexiletine, Tacrine, Thiabendazole, Zileuton

Inducers:

Montelukast, Phenytoin, Rifampin, Ritonavir, **Teriflunomide**

13.2. APPENDIX 2: IMMUNOSUPPRESSORS AND/OR IMMUNOMODULATORS

Abatacept, Abetimus, Adalimumab, Afelimomab, Alefacept, Alemtuzumab, Anakinra, Apremilast, Azathioprine, Baricitinib, Basiliximab, Begelomab, Belatacept, Belimumab, Briakinumab, Brodalumab, Canakinumab, Certolizumab pegol, Cladribine, Cyclosporine, Daclizumab, Dimethyl fumarate, Eculizumab, Efalizumab, Emapalumab, Etanercept, Everolimus, Fingolimod, Glatiramer, Golimumab, Guselkumab, Gusperimus, Infliximab, Interferon, Ixekizumab, Leflunomide, Lenalidomide, Methotrexate, Muromonab, Mycophenolic acid, Natalizumab, Ocrelizumab, Ozanimod, Pirfenidone, Pomalidomide, Rilonacept, Sarilumab, Secukinumab, Siltuximab, Sirolimus, Sirukumab, Tacrolimus, Teriflunomide, Thalidomide, Tildrakizumab, Tocilizumab, Tofacitinib, Ustekinumab, Vedolizumab, Voclosporin.