CLINICAL STUDY PROTOCOL
ABX464-102

Sponsor:	ABIVAX 5, rue de la Baume 75008 Paris FRANCE
Investigational product:	ABX464
Product code:	ABX464
Therapeutic indication:	A follow-up Phase IIa study to evaluate the long-term safety and efficacy profile of ABX464 given at 50 mg once daily in subjects with Moderate to Severe Active Ulcerative Colitis.
EudraCT number:	2017-003284-35
Study code:	ABX464-102
Version number:	7.0
Release date:	February 07th, 2022

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Study code	ABX464-102
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Detailed Title	A follow-up Phase IIa study to evaluate the long-term safety and efficacy profile of ABX464 given at 50 mg once daily in subjects with Moderate to Severe Active Ulcerative Colitis.
Study Phase	Phase IIa
Coordinating Investigator	***Prof. Severine Vermeire*** University Hospitals Leuven - campus Gasthuisberg 3000 Leuven Belgium
Sponsor	**ABIVAX** 5 rue de la Baume 75008 Paris
Date/Version	February 7th, 2022 / Version 7.0

CONTACTS

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Coordinating investigator	**Prof. Severine Vermeire** University Hospitals Leuven - campus Gasthuisberg 3000 Leuven Belgium
Statistical Analysis	
Study Conduct, Data management	
Imaging Central Review	
miRNA-124 determination	
Pharmacovigilance	

INVESTIGATOR AGREEMENT PAGE

EudraCT number 2017-003284-35

Detailed Title: A follow-up Phase IIa study to evaluate the long-term safety and efficacy profile of ABX464 given at 50 mg once daily in subjects with Moderate to Severe Active Ulcerative Colitis.

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 subjects is jeopardized.
- To conduct the study in accordance with the Good Clinical Practice ICH E6 (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, 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: _____

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
AESI	Adverse event of special interest
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvate transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the plasma concentration
BMDM	Bone Marrow Derived Macrophages
CBC	Cap Binding Complex
C_{max}	peak plasma concentration
CPK	Creatine PhosphoKinase
CRF	case report form
CRP	C-Reactive Protein
CTC-AE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DSS	Dextran Sodium Sulfate
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
ESR	Erythrocyte Sedimentation Rate
F_{rel}	relative bioavailability
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GLS	Global Longitudinal Strain
GM	geometric mean
H	hours
HIV	Human Immunodeficiency Virus
HR	heart rate
hs	Hyper sensitivity
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICF	informed consent form
ICH	International Conference on Harmonization
ICVSC	Independent Cardiovascular Safety Committee
IEC	Independent Ethics Committee
Il-6	Interleukin 6
IL-22	Interleukin 22
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intra-Uterine Device
LFTs	Liver Function Tests
LPS	Lipopolysaccharide
LVEF	Left Ventricle Ejection Fraction
Max	maximum
MCS	Mayo Score
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	minimum
miR	micro-RNA
mL	milliliter
NOAEL	No Observed Adverse Effect Level
NT-ProBNP	N-terminal pro-brain natriuretic peptide
o.d.	Once Daily
PBMC	Peripheral Blood Mononuclear Cells
PCSA	potentially clinically significant abnormalities
PD	pharmacodynamics
PK	pharmacokinetics
PP	Per Protocol
qPCR	Quantitative Polymerase Chain Reaction
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
RV	Right Ventricle
RNA	Ribonucleic Acid
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SF-36	Quality of Life Questionnaire
STAT-3	signal transducer and activator of transcription 3

$t_{1/2}$	terminal half-life
TEAE	treatment emergent adverse event
t_{lag}	interval between administration time and the sampling time preceding the first concentration above the limit of quantification
TMS	Total Mayo Score
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
ULN	Upper Limit of Normal range
WOCBP	Women of Child Bearing Potential

SYNOPSIS

Study n°	ABX464-102	**Clinical Phase**	IIa
		Type of Study	Follow-up Study
Study title	A follow-up Phase IIa study to evaluate the long-term safety and efficacy profile of ABX464 given at 50 mg once daily in subjects with Moderate to Severe Active Ulcerative Colitis.		
Short title	Follow-up study in Moderate to Severe Active Ulcerative Colitis subjects.		
Investigators and study centers	Active sites from previous study (ABX464-101) located in Belgium, Hungary and Poland.		
Study period	Q4 2017 – Q3 2022		
Investigational product	ABX464 is a small molecule that binds the cap binding complex (CBC), comprised of two proteins CBP20 and CBP80, within the cell nucleus. This binding leads to an increased expression of a single micro-RNA (miR-124) by impacting the splicing of a single long non-coding RNA. Because of its action on this single splicing event, leading to an increase in miR-124, a microRNA with potent anti-inflammatory properties, ABX464 potentially has broad applicability across a variety of inflammatory diseases. ABX464 is currently under investigation as a potential treatment for Rheumatoid Arthritis (RA) and inflammatory bowel diseases (IBD). As of 30 November 2021, 1023 subjects have received ABX464, according to various administration schedules, in all completed, and ongoing open-label clinical studies across all indications. Out of these 1023 subjects, 830 subjects have been dosed with ABX464 50mg once daily (od) including 240 subjects for longer than 6 months with 197 for more than a year. In addition, 36 subjects have received ABX464 or placebo in ongoing blinded clinical study (ABX464-921). All doses tested were well tolerated.		
Study Design and Methodology	This study is an open-label study aiming at evaluating the long-term safety and the efficacy profile of ABX464 given once a day (o.d) at 50 mg in subjects who have been previously enrolled in the ABX464-101 clinical study (induction study) and who are willing to continue their treatment. All subjects will receive ABX464 given at 50 mg o.d irrespective of their previous treatment received in the ABX464-101 study (i.e. ABX464 or Placebo). The actual treatment received by a subject throughout the previous study (ABX464-101) will not be known at the time the subjects enter this follow-up study. The enrolment in this follow-up study will be based on the willingness of the subject to carry on his/her participation and also based on investigator's judgement. Subjects will be treated with ABX464 for an overall period of 48 months. Subjects will be followed up weekly during the first month, every two weeks during the second month and then on a monthly basis until M24, then quarterly from M24 to M48. At M48, depending on their clinical response, eligible patients willing to continue study treatment will be offered to take part into a long term follow up safety study (ABX464-108 study). ABX464-108 study is a separate study requiring health authorities and ethics committees' approval. If patients are not eligible to pursue treatment in this long-term follow-up study, they will be followed for 4 additional weeks for safety purposes before End of study Visit.		
Study Objectives	**Primary Objective** The primary objective of the study is to evaluate the long-term safety of ABX464 given at 50 mg once daily in subjects with Moderate to Severe Active Ulcerative Colitis. **Secondary Objectives** The secondary objectives are: ▪ To evaluate the long-term effect of ABX464 on clinical and endoscopic remission in subjects with Moderate to Severe Active Ulcerative Colitis assessed by the Mayo Score (MCS). ▪ To evaluate the long-term effect of ABX464 on inflammatory markers (C-Reactive Protein (CRP), Calprotectin and Erythrocyte Sedimentation Rate (ESR) ▪ To evaluate the long-term of ABX464 on Quality of Life (QoL) measured by the SF-36 questionnaire in subjects with Moderate to Severe Active Ulcerative Colitis until M24.		

Study n°	ABX464-102	**Clinical Phase**	IIa
		Type of Study	Follow-up Study
	The echocardiography objective is: To evaluate the effect of ABX464 on cardiac function as assessed through echocardiograms.		
Study Endpoints	**<u>Primary Endpoint:</u>** ▪ Number of incidences of treatment-emergent adverse events in ABX464 treated subjects. **<u>Secondary Endpoints:</u>** ▪ The change from Day 0 in Total Mayo Score. ▪ The change from Day 0 in Partial Mayo Score. ▪ The time to UC worsening. ▪ The change from Day 0 in fecal calprotectin, CRP levels and ESR. ▪ The scores and changes from Day 0 in SF-36 Questionnaire scores. ▪ The miR-124 expression at month 12, month 36 and month 48. ▪ The number of incidences of treatment-emergent serious adverse events. ▪ The number of incidences of treatment-emergent adverse events of special interest. ▪ The number of incidences of adverse events leading to investigational product discontinuation. ▪ The number of incidences of specific laboratory abnormalities. ▪ Percentage of subjects reaching clinical remission at M12, M36, and M48. ▪ Percentage of subjects reaching clinical response at M12, M36, and M48. ▪ Percentage of subjects reaching endoscopic improvement at M12, M36, and M48. ▪ Percentage of subjects reaching endoscopic remission at M12, M36, and M48. ▪ Percentage of subjects reaching corticosteroid-free clinical remission at M12, M36, and M48. *The echocardiography secondary endpoints are:* ▪ Absolute (%) change-from-previous echocardiogram of Left ventricle Ejection Fraction (LVEF) as measured by 2-dimensional echocardiography ▪ Number of subjects with a clinically relevant reduction (change-from-previous echocardiogram) of LVEF, defined as by > 10% reduction (absolute percentage points) to a value < 50% ▪ Absolute (%) change in Global Longitudinal Strain (GLS) from-previous echocardiogram ▪ Number of subjects with a relative percentage reduction in GLS by > 15% from the previous value ▪ Number of subjects with a reduction of LVEF > 10% (absolute percentage points) to a value ≥ 50% with an accompanying fall in GLS > 15% ▪ Number of subjects with a reduction in LVEF by > 10% (absolute percentage points) to a value ≥ 50% ▪ Changes from previous echocardiography of other echocardiographic parameters as described in a standard protocol, including 2-dimensional volumes, RV size and systolic function and valve function.		
Main Selection Criteria	**Inclusion criteria:** **A subject will be eligible for inclusion in this study only if ALL of the following criteria apply:** ▪ Subjects previously enrolled in the ABX464-101 clinical study who have completed the initial 2-month treatment phase; ▪ Subjects able and willing to comply with study visits and procedures; ▪ Subjects with hematological and biochemical laboratory parameters as follows at the D56 visit of the ABX464-101 study: o Hemoglobin > 9.0 g dL-1; o Absolute neutrophil count ≥ 750 mm^{-3}; o Platelets ≥ 100,000 mm^{-3};		

Study n° ABX464-102	**Clinical Phase** IIa **Type of Study** Follow-up Study
	○ Total serum creatinine ≤ 1.3 x upper limit of normal (ULN); ○ Creatinine clearance > 50 mL min-1 by the Cockcroft-Gault equation; ○ Total serum bilirubin < 1.5 x ULN; ○ Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 1.5 x ULN; ▪ Subjects should understand, sign and date the written voluntary informed consent form at the enrolment visit prior to any protocol-specific procedures being performed; ▪ Females and males receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 6 months after end of study or early termination. Contraception should be in place at least 3 months prior to study participation. 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 an 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 participants should use condoms and should not donate sperm as long as contraception is required. ▪ **Exclusion Criteria:** **The following criterion should be checked at the time of screening. If this exclusion criterion applies, the subject will not be included in the study:** ▪ Any condition, which in the opinion of the investigator, could compromise the subject's safety or the adherence to the study protocol.
Medications	**Mandatory and/or allowed Concomitant Medications:** ▪ ABX464 administered once daily at 50 mg ▪ Oral 5-aminosalicylic acid at stable dose. ▪ Immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate at stable dose. ▪ Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) at stable dose. ▪ COVID-19 vaccines are allowed. **Prohibited Concomitant Medications:** ▪ Anti-tumor necrosis factor (TNF) therapies. ▪ Vedolizumab. ▪ JAK inhibitors. ▪ Topical corticosteroids and topical 5-aminosalicylic acid preparations. ▪ Cyclosporine and tacrolimus. ▪ Drugs that could interact with ABX464 should be avoided especially the CYP1A2 inducers/inhibitors. The following CYP1A2 inducers/inhibitors are prohibited during the whole course of the study (ciprofloxacin, enoxacin, fluvoxamine, montelukast, phenytoin, rifampicin, ritonavir, teriflunomide). The UGT1A9 inhibitors and OAT P1B1/P1B3 inhibitors/substrates that could interact with ABX464 and its metabolite ABX464-N-Glu should also be avoided. ▪ Use of any investigational or non-registered product within 3 months preceding Day 0 except ABX464.
Study discontinuation	Subjects who are not found eligible or not willing to enter the ABX464-108 study are not considered as prematurely discontinued as they have completed the scheduled treatment of ABX464-102 study. Subject's study discontinuation could occur for the following reasons: ▪ Investigator's decision;

Study n° ABX464-102	**Clinical Phase** IIa **Type of Study** Follow-up Study
	▪ An Adverse Event or an intercurrent condition that preclude continuation of treatment; ▪ Specifically, an increase ≥ 3.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or an increase ≥ 2.0 x ULN in Alkaline phosphatase or in total bilirubin requires close observation with repeating liver enzymes and serum bilirubin tests two times weekly and clinical investigation to understand the etiology of this elevation. Frequency of retesting can decrease to once a month if abnormality stabilizes after the initial two weeks of follow-up and if the patient is asymptomatic. Discontinuation of the study treatment should occur if: • ALT or AST > 8xULN • ALT or AST > 5xULN for more than 2 weeks • ALT or AST > 3xULN and total bilirubin > 2xULN or INR>1.5 • ALT or AST > 3xULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%); ▪ Severe (grade 3 or higher) infection, a severe (grade 3 or higher) opportunistic infection, or sepsis; o Any cardiac AESI or condition diagnosed during the course of the study and assessed by the clinical adjudication committee as changing the risk/benefit balance for the subject; o New onset of acute pancreatitis; o Malignancies (including non-melanoma skin cancers); o Any relevant toxicity or negative change in the risk/benefit assessment leading to an unacceptable risk for the subject or any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment. This may be applicable but is not limited to the following cases: occurrence of AEs which character, severity or frequency is new in comparison to the existing risk profile, or clinically significant abnormal laboratory results, including new onset anemia (defined as a hemoglobin decrease >2 g/dL from baseline or hemoglobin <8 g/dL ▪ Worsening of the UC defined as a 2-point increase in the pMMS, with pMMS ≥ 4 on 2 separate occasions 7 day-apart and confirmed by an endoscopy sub score of 2 points or higher; subject who would experience a treatment failure during the study may be withdrawn at any time. S/he will have to be treated according to standard of care as soon as s/he is discontinued from study treatment because of study withdrawal; ▪ Withdrawal of consent; ▪ Pregnancy; ▪ Patients included with a history of cardiac ischemic disease and/or congestive heart failure will be discontinued from the study, will perform the End of Study Visit 4 weeks after last study drug administration and will then be treated according to the standard of care upon study treatment interruption. ▪ Administrative reasons from Sponsor.
Data Safety Monitoring Board (DSMB) - Independent Cardiovascular Safety Committee (ICVSC)	A Data Safety Monitoring Board with expertise and experience in the management in UC will review the safety of the trial on a monthly basis until December 2019 and then quarterly from January 2020 onwards. An Independent Cardiovascular Safety Committee (ICVSC), comprised of 3 cardiologists with experience from drug development, will be formed as detailed in the Charter. The ICVSC will be responsible for an on-going evaluation of cardiac adverse events of special interest (Cardiac AESIs), for treatment emergent echocardiographic findings, and for treatment emergent changes of cardiac safety biomarkers (as detailed above). The ICVSC will review cardiac adverse events on an on-going basis, meet regularly and provide recommendations to Sponsor and DSMB regarding study procedures and conduct.
Sample Size calculation	Not applicable / Maximum 30 subjects (i.e. ABX464-101's sample size)
Statistical Methods	**Safety:**

Study n° ABX464-102	**Clinical Phase**	IIa
	Type of Study	Follow-up Study
	Analysis of safety will be performed on the safety data set consisting in all subjects 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 Common Terminology Criteria for Adverse Events "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 potentially clinically significant abnormalities (PCSAs) determined upon investigator considerations. 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, echocardiography parameters, vital signs, and ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Number of subjects with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables**.** **Efficacy:** Efficacy results will be presented descriptively; proper tests will be performed if appropriate.	

1. INTRODUCTION AND STUDY RATIONALE

1.1. Ulcerative Colitis (UC)

1.1.1. Disease

Ulcerative colitis (UC) is a chronic inflammatory condition causing continuous mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, which is characterized by a relapsing and remitting course.

UC is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in the developed countries of the world.

The precise etiology is unknown and therefore medical therapy to cure the disease is not yet available.

1.1.2. Management of subjects

Subjects may live with a considerable symptom burden despite medical treatment (66% describe interference with work and 73% with leisure activities[1] in the hope that the etiology of ulcerative colitis will shortly be revealed, and a cure emerge.

Although most subjects present with mild-to-moderate UC, 10% of subjects initially present with severe disease. Additionally, approximately 15% of subjects will develop a severe flare during the course of their lifetime. Both the American College of Gastroenterology practice guidelines and the European Crohn's and Colitis Organization position statements define severe colitis similarly as the passage of six or more stools per day with evidence of systemic toxicity (e.g., fever, tachycardia, anemia or elevated ESR) [2,3].

Subjects with acute severe UC require hospitalization for optimal management owing to the seriousness of their illness. Although rates of death in severe UC have dropped by up to 25% with the adoption of more aggressive monitoring and treatment [4] acute severe colitis is still associated with a measurable mortality [5].

The use of intravenous steroids and improved surgical techniques probably explain much of the reduction in mortality associated with acute severe UC observed in the decades since their introduction [6].

Severe UC should be considered a medical emergency, and subjects require close monitoring of stool frequency and vitals symptoms. Serial abdominal examinations and plain radiographs should be performed.

The cornerstone of management of severe UC remains the use of intravenous corticosteroids, which are effective in the induction of remission in the majority of cases. While many subjects with acute severe ulcerative colitis will respond to a short course of intravenous corticosteroids, up to a third will fail to improve. In these subjects with steroid-refractory colitis, the choice is between rescue medical therapy with ciclosporin, anti-TNF Alpha, vedolizumab or surgery. Anti-tumor necrosis factor (TNF) therapy is effective for the treatment of UC.

Nevertheless, up to 30% of subjects show no clinical benefit, while another 40% lose response over time and need to escalate or discontinue anti-TNF therapy within one year of treatment.

Thus, there is an unmet medical need for novel treatment options for patients with moderate to severe UC.

1.2. ABX464 rationale

1.2.1. Investigational treatment description

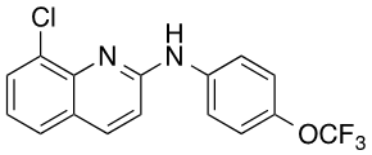
ABX464 is a first-in-class, orally available, small molecule with anti-inflammatory activity which is under investigation as a potential treatment for moderate to severe ulcerative colitis and rheumatoid arthritis.

ABX464 binds the Cap Binding Complex (CBC) comprised of two proteins CBP20 and CBP80, within the cell nucleus. This binding leads to an increased expression of a single micro-RNA (miR-124) by impacting the splicing of a single long non-coding RNA. Because of its action on this single splicing event, leading to an increase in miR-124, a microRNA with potent anti-inflammatory properties, ABX464 potentially has broad applicability across a variety of inflammatory diseases. ABX464 is currently under investigation as a potential treatment for Rheumatoid Arthritis (RA) and inflammatory bowel diseases (IBD).

In humans, ABX464 is conjugated via glucuronidation to ABX464-N-Glu, which contributes the majority of ABX464 plasma exposure. ABX464-N-Glu is pharmacologically active and also binds to the CBC leading to an increase in miR124 expression.

1.2.2. Investigational product description

ABX464 has the following chemical structure:



The chemical name of the 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 g/mol.

The study drug is formulated as hard gelatin, powder-filled capsules (size 01).

1.2.3. Investigational product Mode of Action

ABX464 upregulates MiR-124 in vitro in several cell types

MiR-124 induction by ABX464 in Human Peripheral blood mononucleated cells (PBMCs) has been demonstrated as follows:

- Affymetrix genechip miRNA array 2.0 which contains 15644 miRNA probes representing 1105 miRNA across 131 organisms. The chip also contains 2202 pre-miR probes and 2334 probes for snoRNA and scaRNA.
- TaqMan® Array Human MicroRNA which contains 196 miRNAs.

Both approaches demonstrated that only miR-124 was upregulated by ABX464 treatment across species and that no miRNAs were downregulated. The expression of miR-124 was significantly increased (about 13-fold) by ABX464. MiR-124 was upregulated after ABX464 treatment in both CD4+ and CD8+ T cells.

The effects of ABX464 on miR-124 expression was tested in Human Monocyte-Derived Macrophages (HuMDM). The results demonstrated that using Real Time Taqman quantitative polymerase chain reaction (qPCR), ABX464 is able to up-regulate the expression of miR-124 in HuMDM.

MiR-124 is encoded from three independent genes, *miR-124-1*, *miR-124-2*, and *miR-124-3*, located on human chromosomes 8 and 20. The specific upregulation of miR-124 in CD4+ cells was demonstrated to be the result of the action of ABX464 on the splicing of long non-coding RNA 0599-205 located in *miR-124-1*, one of the three loci expressing miR-124.

ABX464 upregulates miR-124 in treated patients with moderate to severe ulcerative colitis

After 8 weeks of treatment (57 days) with ABX464 at doses of 25, 50 or 100 mg, the number of miR-124 copies in rectal biopsies and in blood were significantly higher in all ABX464 groups compared to placebo (Figure 1 and Figure 2).

Figure 1: MiR 124 induction in rectal biopsies of patients treated with ABX464 in the phase 2b trial (UC)

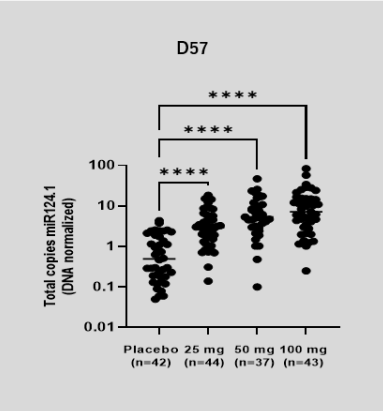
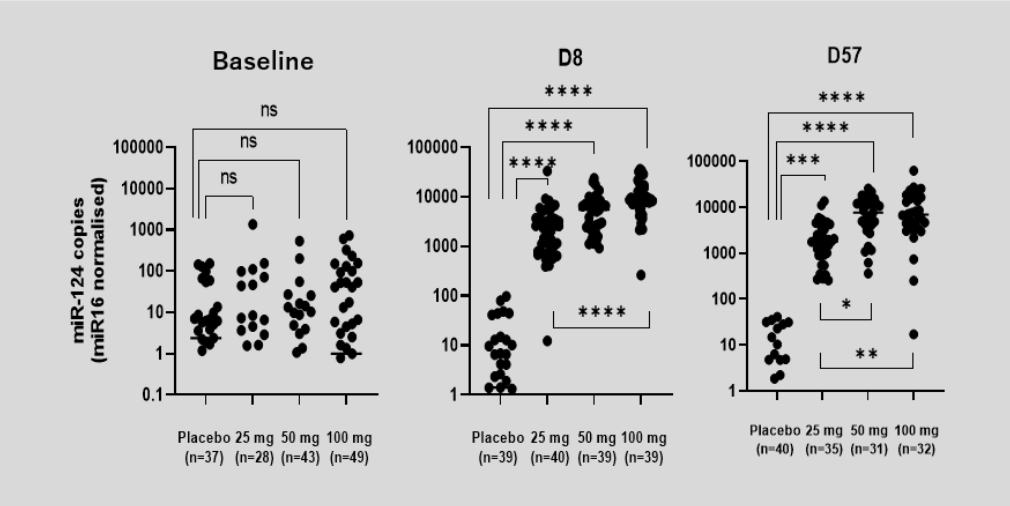


Figure 2 : MiR 124 induction in blood of patients treated with ABX464 in the phase 2b trial (UC)



ABX464 reduces pro-inflammatory cytokines/chemokines

ABX464 reduced the expression of pro-inflammatory chemokines/cytokines MCP1 (-50%), CXCL1 (-20%), IL-10 (-30%), IL-1β (-25%), TNFα (-25%) and IL-6 (-20%) within 4 days of treatment of HuMDM polarized to M1 phenotype.

<u>In vivo evidence for the role of ABX464 in inflammation</u>

ABX464 decreases pro-inflammatory cytokines

The results observed in HuMDM were confirmed in vivo in the mouse model of Dextran Sulfate Sodium (DSS) induced colonic inflammation. Following concomitant 10 days of DSS exposure and ABX464 treatment, ABX464 induced a significant marked reduction of pro-inflammatory cytokines: TNFα (7.5-fold reduction), IL-6 (2-fold reduction), and MCP1 (6-fold reduction in the distal and middle regions) in the supernatant of mouse colons that were incubated for 24 hours in culture medium.

ABX464 decreases the pro-inflammatory Th17 CD4+ cell subset

Th17 cytokines, that include IL-17, IL-23, and IL-22, are often increased in the inflamed intestinal mucosa of active UC and Crohn's disease (CD) patients relative to unaffected regions and healthy controls [7]. In PBMCs, ABX464 treatment did not affect the Treg populations but significantly reduced the number of Th17 and Th1 population and increased Th 2 cells population. Th17 cells are known to differentiate in response to IL-1β, IL6 and IL23 through STAT3 pathway, one of the targets of miR-124 [8]. Proinflammatory Th17 cells are increased in the mesenteric lymph nodes of DSS-exposed mice, ABX464 prevented this increase of Th17 in mesenteric lymph nodes of DSS mice.

IL-17 secretion was also tested during the course of the phase 2b clinical trial in ulcerative colitis (ABX464-103). A statistically significant decrease in IL-17 in the sera of the patients has been shown for patients dosed with ABX464 compared to placebo.

ABX464 reduces disease severity in an acute DSS-induced colitis model

Compared with mice untreated with ABX464, a reduced DSS-induced weight loss was observed in mice receiving ABX464. The weight of ABX464-treated mice returned to pre-treatment levels and the mice displayed decreased disease parameters including smaller and fewer colonic lesions as well as smaller reductions of colon length.

ABX464 decreased macrophages recruitment during acute colitis.

1.2.4. Preclinical data of ABX464

1.2.4.1. 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 sign, 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.

Plasma exposure to ABX464 and ABX464-N-Glu in humans (based on predicted steady-state exposure in ulcerative colitis patients at the highest proposed dose of 100mg) are calculated as being approximately parity (Cmax) to 4-fold (AUC) for ABX464 and 9-fold (Cmax) to 2-fold (AUC) for ABX464-N-Glu exposure as seen in pivotal chronic toxicology studies.

ABX464 had no significant adverse effects on the nervous and respiratory systems, or on cardiovascular function. ABX464 was shown to be non-genotoxic and ABX464-N-Glu was shown to be non-mutagenic.

Genotoxicity:

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.

Reprotoxicity:

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.

Teratogenicity:

ABX464 appears to have teratogenic activity.

Hepatocellular toxicity:

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 one of the animals administered 5mg/kg od, were not considered adverse. Based on this observation, the NOAEL is 5mg/kg od.

No signs of hepatotoxicity related to ABX464 have been observed in any of the patients treated with ABX464 in clinical trials and DILISym evaluation did not predict any risk of liver toxicity for ABX464 and ABX464-N-Glu.

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

1.2.5. Previous clinical experience with ABX464

The effect of ABX464 in humans has been assessed in eighteen clinical trials:

- Completed clinical studies in healthy volunteers (ABX464-001, ABX464-002, ABX464-901, ABX464-902, and ABX464-903) and controlled studies in patients with ulcerative colitis (ABX464-101 and ABX464-103), in patients with rheumatoid arthritis (ABX464-301), in HIV infected subjects (ABX464-003, ABX464-004, and ABX464-005), and in COVID-19 infected patients (ABX464-401).
- Open label studies in ulcerative colitis (ABX464-102, ABX464-104, and ABX464-108) and rheumatoid arthritis (ABX464-302).
- A drug product formulation study (ABX464-905) is ongoing in Healthy Volunteers
- A bioequivalence study (ABX464-921) is ongoing in Japanese Healthy Volunteers.

As of 30 November 2021, 1023 subjects have received ABX464, according to various administration schedules, in all completed, and ongoing open-label clinical studies across all indications. Out of these 1023 subjects, 830 subjects have been dosed with ABX464 50mg once daily (od) including 240 subjects for longer than 6 months with 197 for more than a year. In addition, 36 subjects have received ABX464 or placebo in ongoing blinded clinical study (ABX464-921). Fourteen patients have received ABX464 50mg od for more than 3 years in the UC open label maintenance study (ABX464-102) and 248 patients have received ABX464 50mg for more than 6 months.

ABX464 was rapidly absorbed in healthy volunteers, HIV and UC patients with a Cmax observed approximately 1.5 to 2.9 hours after dosing. Exposure to ABX464 was comparable in all subjects receiving ABX464 at a given dose. PK of ABX464 were linear in the dose range 50-150mg. After repeated administrations of ABX464, an initial decrease in ABX464 AUC was observed and steady state was reached after 4 weeks of treatment.

ABX464 was rapidly metabolised to ABX464-N-Glu. ABX464-N-Glu had a much longer half-life compared to ABX464 (about 100 hours) largely contributing to the high exposures observed.

Food increased ABX464 exposure at least 2.8-fold while exposure to the metabolite was comparable in fed or fasted conditions.

Clinical Efficacy

Completed and ongoing studies with ABX464 in UC are:

- Phase 2a program with an 8-week induction (ABX464-101; completed) and a 4-year maintenance (ABX464-102; ongoing; 52-week interim analysis completed) studies
- Phase 2b program including the 16-week induction (ABX464-103; completed) and an open-label extension (ABX464-104; ongoing) studies

ABX464-103 was a randomized, double-blind and placebo-controlled phase 2b induction study and was conducted from 95 centres in 16 countries. It had three once-daily oral ABX464 treatment groups (25mg, 50mg and 100mg) and one placebo group. 254 patients with moderate to severe active ulcerative colitis were enrolled into the trial. 50% of these patients had inadequate response, loss of response, or intolerance to tumor necrosis factor alpha (TNF-α) inhibitors, vedolizumab, other biologics and/or JAK inhibitors treatments while the other 50% were refractory to conventional treatments. Endoscopies were read centrally and blinded by independent reviewers. Electronic patient diaries were used to promote the reliability of the collection of stool frequency, rectal bleedings and other patient reported outcomes. Gender, clinical, biological and endoscopic parameters were well distributed across placebo and treatment groups at enrolment time. The primary endpoint, i.e. the reduction of the modified Mayo Score from baseline after 8 weeks of treatment was statistically significant for all active treatment groups. ABX464-103 study was completed in April 2021 (LPLV = 16 April 2021).

Table 01 Primary and secondary efficacy endpoints in ABX464-103 study

Week 8 top-line results (ITT[1] population / N= 252)		**Placebo**	**25mg**	**50mg**	**100mg**
Primary Endpoint					
Modified Mayo Score Mean change from baseline	All patients	-1.9	-3.1 *	-3.2 *	-2.9 *
	Bio exposed	-1.0	-2.8 *	-2.9 *	-2.8*
**p-values of <0.05 versus placebo for all dose groups (ANCOVA)*					
Key Secondary Endpoints (not powered to show statistical significance)					
Endoscopic Improvement[a,d]	All patients	8 (13.6%)	20 (34.5%) *	21 (39.6%) *	24 (44.4%) *
	Bio exposed	1 (3.7%)	8 (28.6%) *	7 (30.4%) *	8 (26.6%) *
**p-values of <0.05 versus placebo for all dose groups using a likelihood ratio chi-square test*					
Clinical Remission [b, d]	All patients	8 (12.5%)	17 (27.9%) *	11 (17.5%)	16 (25.0%)
	Bio exposed	1 (3.2%)	6 (20.0%) *	2 (6.7%)	6 (18.8%) *
**p-values of <0.05 versus placebo using a likelihood ratio chi-square test but not according to the predefined Mantel-Haenszel Chi Square test (p<0.1)*					
Clinical Response [c, d]	All patients	23 (35.9%)	40 (65.6%) *	38 (60.3%) *	35 (54.7%) *
	Bio exposed	5 (16.1%)	17 (56.6%) *	13 (43.3%) *	15 (46.8%) *
**p-values of <0.05 versus placebo using a likelihood ratio chi-square test*					
Fecal Calprotectin (µg/g) Mean change from baseline	All patients	-1027.7	-2192.8 **	-2316.8 **	-2280.9 **
**p-values of <0.01 versus placebo (MMRM)					

1 = Intent-to-treat patient population. Drop-out patients were considered as failure for all binary endpoints. Nearest neighbor imputation (as defined in the Statistical Analysis Plan) was used for missing values at week 8 and applied to MMS, clinical remission, and clinical response. Endoscopic improvement rates are presented without imputation (data available at time point).
a = Endoscopic improvement is defined as endoscopic subscore ≤1.
b = Clinical remission (per Modified Mayo Score) is defined as stool frequency subscore (SFS) ≤1, rectal bleeding subscore (RBS) of 0 and endoscopic subscore ≤1.
c = Clinical response (per Modified Mayo Score) is defined as a decrease from baseline in the Modified Mayo Score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1.
d = Evidence of friability during endoscopy confers an endoscopic subscore of 2 or 3

ABX464 was shown to be effective in patients refractory to conventional treatments and, importantly, also in patients with inadequate response, loss of response, or intolerance to biologics and/or JAK inhibitors. These efficacy results warrant the continuation of the development of ABX464 in UC indication.

97.7% of all patients who completed the phase 2b induction study (ABX464-103), irrespective of treatments or treatment outcome during the induction study, enrolled into this subsequent open-label maintenance study to evaluate the long-term safety and efficacy profile of ABX464 for up to two years.

Clinical Safety

During non-clinical studies, the main clinical signs observed in non-clinical studies for ABX464 consisted of, ptyalism and bodyweight loss which was dose proportional and severe in some cases. the main target organs affected were the gastro-intestinal tract and liver with the main macroscopic findings observed as dark foci in the glandular mucosa of stomach, adverse altered cell foci and bile duct hyperplasia in the liver, adverse erosion/ulcer in the forestomach, centrilobular hepatocellular degeneration/necrosis and liver necrosis. Some degree of anemia was found in the 9-month marmoset study with ABX464-N-Glu. Immunosuppression has been observed in a 9-month study with direct dosing of ABX464-N-Glu in cynomolgus monkeys. Two cases of cardiac fibrosis, likely associated with the Marmoset Wasting Syndrome, have been observed in a 9-month study with marmoset monkeys exposed to high doses of ABX464-N-Glu.

As of 30 November 2021, 1023 subjects have received ABX464, according to various administration schedules, in all completed, and ongoing open-label clinical studies across all indications. Out of these 1023 subjects, 830 subjects have been dosed with ABX464 50mg once daily (od) including 240 subjects for longer than 6 months with 197 for more than a year. In addition, 36 subjects have received ABX464 or placebo in the ongoing blinded clinical study (ABX464-921). All doses tested were well tolerated. 38 Serious Adverse Events were reported in all clinical studies, except COVID study (ABX464-401) which are reported separately in this IB. No fatalities were reported in non-COVID indication/population except one fatal case that was a road traffic accident and was unrelated to the study drug.

Anticipated ABX464 adverse events (regardless of their severity)

Frequent gastrointestinal symptoms such as abdominal pain, nausea, vomiting and diarrhea, as well as headaches, are described effects for ABX464, which are dose-dependent, with intensity going from mild to severe, occurring after treatment onset.

Therefore, designated anticipated AEs are:

- Headache
- Nausea
- Vomiting
- Abdominal pain (abdominal pain or upper abdominal pain)
- Diarrhea
- Back pain

Due to safety signals in nonclinical toxicology studies, the following events are monitored as adverse events of special interest in ongoing and future studies with ABX464: anemia, liver function tests abnormalities, serious grade 3 infections and opportunistic infections, malignancies including non-melanoma skin cancers and cardiac events, including biomarkers (blood levels of AST, troponin, CPK and NT-proBNP).

The following events have been observed in clinical studies and are also monitored as adverse events of special interest in ongoing and future studies with ABX464: headaches, skin lesions plus lipase elevation and acute pancreatic disorders.

Healthy volunteers and patients exposed to ABX464 will continue to be monitored with routine ECGs as part of the clinical studies.

Overall, ABX464 is considered to be safe and clinical development is justified.

For further information, please refer to the current Investigator's Brochure.

1.3. Rationale for the clinical study and study design

Phase IIb study (ABX464-101) aimed at evaluating the efficacy and safety of ABX464 given at a fixed dose of 50mg once daily versus placebo in patients with moderate to severe active UC who have failed or are intolerant to immunomodulators, anti-TNFα or corticosteroids was conducted in Belgium, France, Germany, Austria, Poland, Hungary.

32 patients were randomized (23 ABX464 patients/9 placebo). The principal study results are presented below.

A strong efficacy signal was observed with ABX464 50 mg:

- Clinical Remission rate of 35.0 % of ABX464 patients (Placebo = 11.1%)
- Mucosal Healing rate of 50.0 % (p=0.03) of ABX464 patients (Placebo = 11.1%)
- Clinical Response rate of 70.0 % of ABX464 patients (Placebo = 33.0%)

Same results were also observed in Total and Partial Mayo Score, as depicted in the following graphs

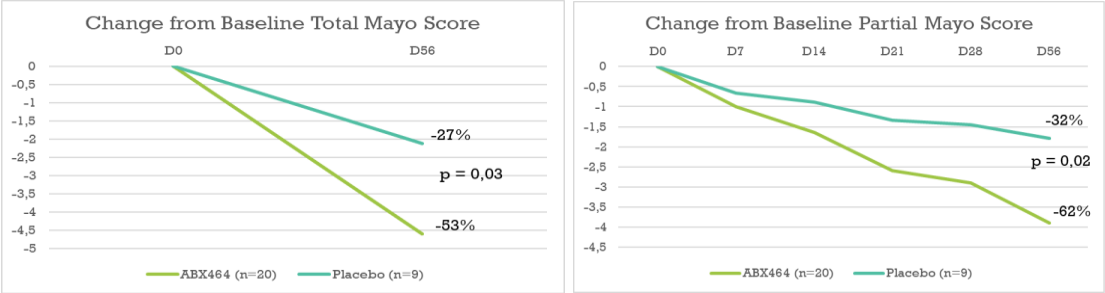


Figure 3: Mean change in Total and Partial Mayo Score in ABX464-101 study

At the end of the completed 2 months induction treatment study, 22 Patients (15 previously treated with ABX464 and 7 on placebo) were enrolled into the open-label maintenance study with ABX464 50mg daily (ABX464-102) regardless of what treatment they had previously received. An interim analysis of this maintenance study was performed after all patients had completed at least 12 months dosing in the maintenance study, with a mean ABX464 treatment duration in the maintenance study of 422 days.

The interim analysis used the Month 12 Per Protocol (M12 PP) dataset which included all subjects that had a Month 12 visit. Of the 22 subjects, 3 subjects were excluded from the M12 PP Set: 2 subjects from the ABX464 induction group (one who withdrew due to lack of efficacy at M1 of the maintenance study and one who was lost to follow-up) and 1 subject from the placebo induction group (grade 2 headache at month 4), resulting in 19 subjects analyzed in the efficacy M12 PP set at baseline. Of the nineteen subjects in the set, sixteen had had a Month 12 endoscopy performed which forms part of the Total Mayo score (TMS).

Clinical remissions obtained at the end of the induction study were durable and the rates further improved during the maintenance phase, as additional subjects achieved clinical remission for 12 months treatment.

All patients who had an endoscopy performed, had an endoscopic sub-score of 0 or 1. 12/16 patients were in clinical remission at month 12.

Mean and median fecal calprotectin and CRP showed continued declines during the maintenance study, though the large variability and small patient numbers requires that the results should be interpreted with caution. The measurement of miR124 relative gene expression by qPCR using whole blood samples was included in both ABX464-101 and -102. A total of 19 patients were sampled on day 0, 28, 56 of ABX464-101 and on day 365 (while in ABX464-102). Statistically significant increases of miR124 expression were observed at all these time points.

No severe or serious adverse reactions were reported. Most adverse events were of mild to moderate intensity. The efficacy and safety results of studies ABX464-101 and ABX464-103 warrant the continuation of the clinical development of ABX464 in this indication.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety of ABX464 given at 50 mg once daily in subjects with Moderate to Severe Active Ulcerative Colitis.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the long-term effect of ABX464 on clinical and endoscopic remission in subjects with Moderate to Severe Active Ulcerative Colitis assessed by the MCS.
- To evaluate the long-term effect of ABX464 on inflammatory markers (CRP, Calprotectin and ESR)
- To evaluate the long-term of ABX464 on Quality of Life (QoL) measured by the SF-36 questionnaire in subjects with Moderate to Severe Active Ulcerative Colitis until M24.

Echocardiography objective is:

- To evaluate the effect of ABX464 on cardiac function as assessed through echocardiograms.

2.3. Primary Endpoint

The primary endpoint of this study is defined as the number of incidences of treatment-emergent adverse events in the ABX464 treated subjects.

2.4. Secondary Endpoints

The secondary endpoints of this study are:

- The change from Day 0 in Total Mayo Score.
- The change from Day 0 in Partial Mayo Score.
- The time to UC worsening.
- The change from Day 0 in fecal calprotectin, CRP levels and ESR.
- The scores and changes from Day 0 in SF-36 Questionnaire scores.
- The miR-124 expression at month 12, month 36 and month 48.
- The number of incidences of treatment-emergent serious adverse events.
- The number of incidences of treatment-emergent adverse events of special interest.
- The number of incidences of adverse events leading to investigational product discontinuation.
- The number of incidences of specific laboratory abnormalities.
- Percentage of subjects reaching clinical remission at M12, M36, and M48.
- Percentage of subjects reaching clinical response at M12, M36, and M48.
- Percentage of subjects reaching endoscopic improvement at M12, M36, and M48.
- Percentage of subjects reaching endoscopic remission at M12, M36, and M48.
- Percentage of subjects reaching corticosteroid-free clinical remission at M12, M36, and M48.

The echocardiography secondary endpoints [9] are:

- Absolute (%) change-from-previous echocardiogram of Left ventricle Ejection Fraction (LVEF) as measured by 2-dimensional echocardiography
- Number of subjects with a clinically relevant reduction (change-from-previous echocardiogram) of LVEF, defined as by > 10% reduction (absolute percentage points) to a value < 50%

- Absolute (%) change in Global Longitudinal Strain (GLS) from-previous echocardiogram
- Number of subjects with a relative percentage reduction in GLS by > 15% from the previous value
- Number of subjects with a reduction of LVEF > 10% (absolute percentage points) to a value ≥ 50% with an accompanying fall in GLS > 15%
- Number of subjects with reduction in LVEF by > 10% (absolute percentage points) to a value ≥ 50%
- Changes from previous echocardiography of other echocardiographic parameters as described in a standard protocol, including 2-dimensional volumes, RV size and systolic function and valve function.

3. INVESTIGATIONAL PLAN

3.1. Study design

3.1.1. Design and methodology

This study is an **open-label** study aiming at evaluating the long-term safety and the efficacy profile of ABX464 given once a day (o.d) at 50 mg in subjects who have been previously enrolled in the ABX464-101 clinical study (induction study) and who are willing to continue their treatment.

All subjects will receive ABX464 given at 50 mg o.d irrespective of their previous treatment received in the ABX464-101 study (i.e. ABX464 or Placebo).

The actual treatment received by a subject throughout the previous study (ABX464-101) will not be known at the time the subjects enter this follow-up study.

The enrolment in this follow-up study will be based on the willingness of the subject to carry on his/her participation and also based on investigator's judgement.

Subjects will be treated with ABX464 for an overall period of 48 months. Subjects will be followed up weekly during the first month, every two weeks during the second month and then on a monthly basis until M24, then quarterly from M24 to M48.

At M48, depending on their clinical response, eligible patients willing to continue study treatment will be offered to take part into a long term follow up study (ABX464-108 study). ABX464-108 study is a separate study requiring health authorities and ethics committees' approval. If patients are not eligible to pursue treatment in this long-term follow-up study, they will be followed for 4 additional weeks for safety purposes before End of study Visit.

3.1.2. Data Safety Monitoring Board – Independent Cardiovascular Safety Committee (ICVSC)

An independent Data Safety Monitoring Board (DSMB), with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee effective protection of subjects, 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 on a monthly basis until December 2019 and then quarterly from January 2020 onwards. Besides, the DSMB may recommend the early termination of the trial at any time if an unacceptable toxicity occurs.

In addition, DSMB will be review all potential causally related Serious Adverse Events within 7 days of the initial report.

The DSMB has only a consultative role; it will inform the sponsor who will decide whether the DSMB recommendation will be followed. A DSMB charter must be available upon submission of the trial (initial protocol) to the respective competent authorities.

An Independent Cardiovascular Safety Committee (ICVSC), comprised of 3 cardiologists with experience from drug development, will be formed as detailed in the Charter. The ICVSC will be responsible for an on-going evaluation of cardiac adverse events of special interest (Cardiac AESIs), for treatment emergent echocardiographic findings, and for treatment emergent changes of cardiac safety biomarkers (as detailed above). The ICVSC will review cardiac adverse events on an on-going basis, meet regularly and provide recommendations to Sponsor and DSMB regarding study procedures and conduct.

3.2. Duration of study participation

Subjects will be enrolled in the present study at Day 0 and will be treated for a treatment overall duration of 48 months.

From ABX464 treatment stop onwards, subjects will be followed-up for one additional month.

4. STUDY POPULATION

4.1. Number of Subjects/Centers

These subjects were enrolled in some of the active sites of the induction study (ABX464-101). These sites are located in, Belgium, Poland and Hungary.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if ALL of the following criteria apply:

- Subjects previously enrolled in the ABX464-101 clinical study who have completed the initial 2-month treatment phase;
- Subjects able and willing to comply with study visits and procedures;
- Subjects with hematological and biochemical laboratory parameters as follows at the D56 visit of the ABX464-101 study:
    - Hemoglobin > 9.0 g dL-1;
    - Absolute neutrophil count ≥ 750 mm^{-3};
    - Platelets ≥ 100,000 mm^{-3};
    - Total serum creatinine ≤ 1.3 x ULN (upper limit of normal);
    - Creatinine clearance > 50 mL min-1 by the Cockcroft-Gault equation;
    - Total serum bilirubin < 1.5 x ULN;
    - Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 1.5 x ULN;
- Subjects should understand, sign and date the written voluntary informed consent form at the enrolment visit prior to any protocol-specific procedures being performed;
- Females and males receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 6 months after end of study or early termination. Contraception should be in place at least 3 months prior to study participation. 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 an 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 participants should use condoms and should not donate sperm as long as contraception is required.

4.2.2. Exclusion Criteria

The following criterion should be checked at the time of screening. If this exclusion criterion applies, the subject will not be included in the study:

- Any condition, which in the opinion of the investigator, could compromise the subject's safety or the 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.

	(D56) D0	***D7***	***D14***	***D21***	***D28***	***D42***	***Day56/M2***	***Mx+1 to M24***	***M27 to M45****	***M48***	***EoS***
Time Window		± 2 days	± 2 days	± 2 days	± 4 days	± 2 days	± 4 days	± 4 days	± 14 days	± 14 days	28 days after ABX464 Stop (± 4 days)
ABX464-101 D56 examinations	X										
Obtained Inform Consent	X										
Check of IN/EX Criteria	X										
Physical Examination		X	X	X	X	X	X	X	X	X	X
Body Weight (kg)		X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X
ECG (12 lead)							X	At Month 24	X	X	X
Blood Pregnancy test (WOCBP)					X		X	X	X[a]	X[a]	X
Hematology + Biochemistry, including NT-proBNP[b]		X	X	X	X	X	X	X	X[b]	X[b]	X[b]
miR-124 blood sample (Paxgene®)								At Month 12	At Month 36	At Month 48	
Mayo score (Total or Partial)		X	X	X	X	X	X	X	X	X	X
Faecal calprotectin					X		X	X	X	X	X
Sigmoidoscopy					As needed		X	At Month 24	At Month 36	At Month 48 [d]	
Cardiac ischemic disease/congestive heart failure medical/treatment history review									X	X	
Echocardiography[c]									X	X	
SF-36 (Questionnaire)					X		X	X			
ABX464 treatment dispensation	X				X		X	X	X		
Adverse Events and CM recording	X	X	X	X	X	X	X	X	X	X	X

* Visits are performed quarterly after M24 (at M27, M30, M33, M36, M39, M42, M45, M48).

[a] Urine pregnancy tests will be provided to WOCBP to perform a pregnancy check every month (between onsite visits)

[b] NT-proBNP blood levels only at Month 42 and 48 and at the End of Study Visit

[c] Echocardiography at the earliest visit, then at Month 42 and 48

[d] Local reading result of sigmoidoscopy need to be available on M48 visit to check eligibility to enter study ABX464-108

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. Day 0 (D56 visit of the ABX464-101 study)

The subject will be informed about the general aspects of the study and will sign the screening informed consent form. The subject number will be allocated once the subject will be created in the eCRF. Only when consent has been given may further study procedures be carried out. During Day 0 visit, the assessments planned as the D56 Visit in the ABX464-101 study protocol should be performed.

In addition, if the subject is eligible for the Follow-up study the following examination should be performed:

- Signed informed consent form;
- Inclusion/exclusion criteria will be verified globally;
- ABX464 IMP dispensation;
- Adverse Events and Concomitant Medications reporting.

5.2.2. Day 7, 14, 21, 42 visits (± 2 days)

The following examinations/procedures should be performed:

- Physical examination and vital signs;
- Body weight;
- Hematology & Biochemistry;
- Partial Mayo Score;
- Adverse Events and Concomitant Medications reporting;
- Schedule next subject visits.

5.2.3. Day 28, Day 56/M2, Mx+1 Visits (28 ± 4 days) until M24

The following examinations/procedures should be performed:

- SF-36 questionnaire (as the first visit procedure);
- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry including blood pregnancy test for all women of childbearing potential;
- Faecal calprotectin dosage;
- Sigmoidoscopy, mandatory only at D56 and at M24
- 12 leads ECG only at D56 and at M24;
- Blood sampling for miR-124 expression at month 12 only:
- Partial or Total Mayo Score;
- ABX464 IMP dispensation
- Adverse Events and Concomitant Medications reporting;
- Schedule next subject visits.

5.2.4. M27 until M45 (Calendar month ± 14 days)

Visits are performed quarterly after M24. Only 7 visits should be performed at M27, M30, M33, M36, M39, M42, and M45. The following examinations/procedures should be performed:

- Review of the subject's medical history at the earliest opportunity to discontinue subjects with history of cardiac ischemic disease and/or congestive heart failure; If the patient needs to be discontinued, she/he will perform the End of Study Visit 4 weeks after last study drug intake.
- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry including blood pregnancy test for all women of childbearing potential and NT-proBNP (at Month 42 only);
- Faecal calprotectin dosage;
- 12 leads ECG;
- Blood sampling for miR-124 expression at month 36 only
- Partial Mayo Score;
- Total mayo score (only at M36);
- ABX464 IMP dispensation;
- Adverse Events and Concomitant Medications reporting;
- Sigmoidoscopy, mandatory at M36;
- Echocardiography at the earliest visit, and at M42;

- Schedule next subject visits.

5.2.5. M48 (Calendar month ± 14 days)

Visit M48 is the last visit in this study before entering the long-term follow-up study ABX464-108. If the patient is not eligible to enter this ABX464-108 study, she/he will perform the End of Study Visit (EoS) 4 weeks after last study drug intake.

The following examinations/procedures should be performed:

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry including blood pregnancy test for all women of childbearing potential and NT-proBNP;
- Faecal calprotectin dosage;
- 12 leads ECG;
- Blood sampling for miR-124 expression
- Partial Mayo Score;
- Total mayo score;
- Adverse Events and Concomitant Medications reporting;
- Sigmoidoscopy, mandatory;
- Echocardiography
- Schedule the EoS visit (if patient doesn't enter the study ABX464-108)

Nota bene:

- **The last treatment intake in study ABX464-102 should be the day before this visit M48.**
- **The local reading result of sigmoidoscopy need to be available on M48 visit to check eligibility to enter study ABX464-108.**The sigmoidoscopy can be performed within 14 days before the visit but not after the visit. If the sigmoidoscopy results (local reading) are not available on M48, the patient will be considered not eligible to enter the ABX464-108 study and will performed the end of study visit 28 days (+4 days) after M48.

5.2.6. End of Study Visits

This EoS visit should be performed 28 days (+4 days) after the last study treatment dosing, or if a subject meets a discontinuation criterion before. From the last dosing day, subjects will be treated according to standard of care.

Following examinations/procedures should be performed:

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry including blood pregnancy test for all women of childbearing potential and NT-proBNP;
- Partial Mayo Score;
- 12 leads ECG;
- Faecal calprotectin dosage;
- Adverse Events and Concomitant Medications reporting.

NB: In case of premature discontinuation occurring during the treatment phase the above examinations should be performed as an End of Study Visit 4 weeks after treatment interruption.

After the end of study visit, patients will be treated according to the local standard of care.

5.3. Detail of the study assessments

5.3.1. Echocardiography

Since enrolment is completed at the time of this amendment, drug-free baseline measurements are not available.

All patients ongoing in the study have already undergone Month 36 visit. Therefore, an echocardiography will be performed at the earliest visit and then at Month 42 and Month 48. Echocardiography will be performed locally. Procedures will be standardized for optimized video acquisition at clinical sites. Sites will receive an Echocardiography Manual that includes detailed instructions regarding image acquisition.

Two-dimensional echocardiography measurements will be assessed during the study. The following standard parameters - pertinent to the assessment of changes in cardiac function will be assessed:

- Left Ventricular Ejection Fraction (LVEF%)
- Left Ventricular end systolic/end diastolic volumes
- Left Ventricular septal/posterior wall thickness
- Left Ventricular Mass/Mass indexed
- Left Ventricular Global Longitudinal Strain (GLS)
- Left Atrial volume
- Doppler assessment (Mitral E/A ratio, Stroke Volume, Cardiac Output, Tissue Doppler Imaging)
- Valvular assessment for regurgitation/stenosis
- Right ventricular size

Specific attention will be brought to potential changes from previous assessment in LVEF and GLS. All echocardiographic parameters will be presented descriptively and will be reviewed by the Independent Cardiovascular Safety Committee (ICVSC).

5.3.2. Cardiac ischemic disease/congestive heart failure) medical / treatment history review

- A retrospective review of medical history to search for cardiac ischemic disease and/or congestive heart failure will be done at the next possible visit of the subject as enrolment is finished at the time of this amendment. Patients with a history of or treated for cardiac ischemic disease and/or congestive heart failure will have to be discontinued from the study. If the patient needs to be discontinued, she/he will perform the End of Study Visit 4 weeks after last study drug administration and will then be treated according to the standard of care upon study treatment interruption.

5.3.3. Physical Examination and Vital Signs

A routine physical examination (including body weight) will be done at each study visit. 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 documented as adverse event.

Measurements of vital signs will be done at each visit (Blood pressure, Heart Rate, Body temperature). The subject should rest supine for at least 10 minutes prior to measurements. The measurements can be performed either in sitting or supine position of the subject. 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 subject.

The investigator should ensure that each parameter outside the normal range is assessed for clinical significance. For any deviation assessed clinically significant, the investigator has to document the change as an adverse event (AE) in the eCRF.

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 considers the change to be clinically significant, even if the absolute value is within the alert limit or reference range.

5.3.4. Pregnancy

For all female subjects of childbearing potential, a blood pregnancy test (beta human chorionic gonadotropin [HCG]) will be each month and quarterly after Month 24. From Month 24 onwards, monthly urine pregnancy test will be provided to WOCBP to check for pregnancy between on-site visits. In case of positive pregnancy testing, detailed procedures can be found in section 8.4.2.

5.3.5. ECG

Electrocardiograms have to be done at Day 56, quarterly from M24 to M48 and at EoS visits. At least a 12-lead ECG with recordings of at least 6 action potentials in lead II (paper speed 25mm/s, amplitude 10mm/mV) has to be done in a resting position. Prior to the recording the subject should be at rest for at least five minutes. Resting ECG should be performed before any examinations.

The ECG printout will be reviewed by the investigator and a signed and dated copy of the ECG will be attached to the medical file. The original ECG printouts are considered as source data and should be stored at site. In case thermal paper is used, a copy of the original ECG must be kept as well. All abnormal findings must be documented in the CRF. Any clinically relevant findings compared to ECG done at the EoS visit of the previous study (ABX464-101) must be documented as adverse events.

5.3.6. miR-124 expression level determination

ABX464 up-regulates miRNA in PBMCs, making of this micro-RNA a potentially useful biomarker for ABX464 treatment monitoring. Determination of miRNA level in total blood will be performed at Month 12, Month 36 and Month 48 in order to assess the sustainability of the up regulation observed during the induction study. Assays for miRNA determination will be conducted by a specialized central laboratory.

Total blood in PAXgene® tubes will be used according to lab manual instructions.

5.3.7. SF-36 questionnaire (SF-36)

The SF-36 questionnaire is a self-administered questionnaire containing 36 items which takes about five minutes to complete. It measures health on eight multi-item dimensions, covering functional status, well-being, and overall evaluation of health. SF-36 will be filled in by the subjects on a monthly basis until M24 prior to any study procedures.

5.3.8. Partial/Total Mayo Score

The Total Mayo score is the most commonly used index in clinical trials and consists of 4 items: stool frequency, rectal bleeding, flexible sigmoidoscopic examination, and a physician global assessment of disease activity (Appendix#3).

A non-invasive 9-point Mayo or partial Mayo Score (pMS) incorporates stool frequency, rectal bleeding, and the physician's global assessment of disease activity. The partial Mayo Score has been found to correlate closely with the full Mayo score and to independently have strong discriminative and construct validity and responsiveness to change in disease activity.

Modified Mayo Score (MMS) consists of 3 items: stool frequency, rectal bleeding, flexible sigmoidoscopic examination) and partial Modified Mayo Score (pMMS) consists of only 2 items: stool frequency and rectal bleeding. Either the Partial or the Total Mayo score will be completed at each subject visit by the Investigator.

Partial modified or modified Mayo score will also be used in descriptive analysis and for efficacy evaluation.

5.3.9. Sigmoidoscopy

A Sigmoidoscopy will be performed in all subjects at Day 56/M2, Month 24, Month 36, and Month 48 (i.e. Study procedure).

In addition, monthly sigmoidoscopies could be performed if deemed necessary by the investigator (Until month 24). In such a case, the endoscopy rating will be reported in the eCRF (Total MCS).

Sigmoidoscopies procedures (or colonoscopies if applicable) at Month 24, Month 36, and Month 48 will be standardized for optimized video acquisition at clinical sites. Sigmoidoscopies should be performed according to the Central Imaging Management System Charter. Central Imaging Management System will be provided including a central image database. Once uploaded, video data will be analyzed for quality and resolution prior to independent review by an expert central reader. Study videos will be scored separately using the Mayo Clinic Score (excluding friability) for all time points by central readers.

The local reading result of sigmoidoscopy need to be available on M48 visit to check eligibility to enter study ABX464-108. The sigmoidoscopy can be performed within 14 days before the visit but not after the visit. If the sigmoidoscopy results (local reading) are not available on M48, the patient will be considered not eligible to enter the ABX464-108 study and will performed the end of study visit 28 days (+4 days) after M48.

5.3.10. Clinical remission, clinical response, and corticosteroid-free clinical remission

The following remission and response will be assessed at M12, M24, M36 and M48:

Clinical remission is achieved when all the following criteria are met in the components of the Mayo Score:

- rectal bleeding sub-score = 0
- central endoscopy sub-score <= 1
- stool frequency sub-score <= 1.

Clinical response is defined as:

- reduction in Total Mayo Score of at least 2 points and >= 30 percent from baseline
- with an accompanying decrease in rectal bleeding sub-score of >= 1 point or absolute rectal bleeding sub-score of <= 1 point.

Corticosteroid-free clinical remission is defined as clinical remission at M12, M24, M36 and M48, and concomitant corticosteroid free for ≥ 12 weeks prior to these timepoints among patients with clinical remission after 8 weeks of induction treatment (at baseline of ABX464-102 study).

5.3.11. Endoscopic improvement and endoscopic remission

Endoscopic improvement is achieved if the Mayo central endoscopic sub-score is 0 or 1.

Endoscopic remission is defined as Mayo central endoscopic sub-score = 0.

5.3.12. Hematology and biochemistry

For hematology and biochemistry local laboratory will be used. All lab dosages will be done locally.

Any hematology and biochemistry safety sample (Total bilirubin, AST/ALT, Alkaline phosphatase, Lipase INR, Prothrombin, high-sensitivity (hs) Troponin I & T, CPK and NT-proBNP) that does not have a result reported at any visit must be repeated (e.g. if sample is hemolyzed). The sample should be repeated as soon as possible (and recorded as an unscheduled visit in the eCRF).

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 displays the clinical laboratory parameters that must be measured.

Table 2: Laboratory Tests

HEMATOLOGY	BIOCHEMISTRY	STOOLS
Hemoglobin	Sodium	Faecal calprotectin
Hematocrit	Potassium	
WBC	Chloride	
Neutrophils	Calcium	
Lymphocytes	Phosphate	
Monocytes	Glucose	
Eosinophils	BUN or urea	
Basophils	Creatinine	
Platelet count	AST	
ESR	ALT	
Fibrinogen	GLDH	
Prothrombin time and/or INR	Lipase	
	Alkaline phosphatase	
	gGT	
	Total bilirubin	
	Total protein	
	Albumin	
	LDH	
	CRP	
	CPK	
	High-sensitive Troponin T and/or I	
	NT-proBNP	
	Amylase	

The indicative volumes drawn per study visit are presented in the following table.

	COLLECTION TUBE
Hematology (Hemoglobin, Hematocrit, Red Cell Count, MCV, MCHC, Platelets, White cell count with diff.)	2mL EDTA tube
Fibrinogen and Prothrombin Time and/or INR	4,5 mL Na-citrate tube
NT-proBNP	2mL K2 EDTA tube
Biochemistry panel incl CRP, Serum Pregn. and hs Troponin (Iand/orT)	3.5mL serum gel tube
miR-124 determination at M12, M36, M48 only	5mL of total blood (PAXgene tube)
ESR	5mL ESR tube

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 subjects enrolled in this follow-up study consists of capsules containing ABX464 given orally once daily.

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 50 mg of ABX464 drug substance in the form of granulate prepared with a number of common excipients (microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate and colloidal silica). It is supplied in high-density polyethylene bottles closed with high-density screw caps.

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

Primary packaging labelling as well as Qualified Person release of the IMP are performed at the following site:

CREAPHARM CLINICAL SUPPLIES (previously SODIA)
Avenue Robert Schuman
51 100 REIMS

The study drug should not be stored above 30°C (86°F) and should not be frozen or refrigerated.

6.3. Administration and Dosing

6.3.1. Administration of the investigational product

Subjects will be dosed with a daily dose of 50 mg that is 1 capsule every day.

Subjects will be orally dosed in fed condition (regular breakfast) with a cup of water.

A subject diary, in which the subject should report the number of capsules taken and the intake time, will be given to the subject at baseline. Moreover, this diary will enable the subject to report also potential discomfort or side effects s/he could experience.

The last study treatment intake should be the day before M48 visit.

6.3.2. Guidelines for treatment postponement and dose modifications

No intra-subject dose escalation/dose adjustment are allowed.

6.4. Method of Assigning Subjects to Treatment Arms

All subjects will be assigned a unique and incremental subject Identification (ID) number (i.e. the same than the one used in the ABX464-101 study). Subject IDs will be unique (i.e. reallocation of the ID will not be permitted). The format will be a seven-digit number as follows: ABX-country/site number (4 digits) – subject number (3

digits). The latter 3-digit subject number will be assigned according to the subject's order of inclusion in the center.

Study treatment dispensation will be performed at each study visit. In all cases, subject should return his/her used and unused bottles at each study visit for a compliance check.

6.5. Packaging

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

6.6. Storage

ABX464 will be shipped to the investigational site at ambient temperature. The study drug should not be stored above 30°C (86°F) and should not be frozen or refrigerated.

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.

6.7. 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.

6.8. Prior and Concomitant Medication

6.8.1. Allowed concomitant treatment

Mandatory and/or allowed Concomitant Medications are:

- ABX464 once daily at 50 mg.
- Oral 5-aminosalicylic acid at stable dose.
- Immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate at stable dose.
- Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) at stable dose.
- COVID-19 vaccines are allowed.

Potential other concomitant medications should be kept at constant dose during the course of the study and properly reported in the medical file of the subject and the eCRF.

This information should include the name of the medication (international nonproprietary name), daily dosage, duration and indication.

6.8.2. Prohibited concurrent medications

The following drugs are prohibited during the course of the study.

- Anti-tumor necrosis factor (TNF) therapies.
- Vedolizumab.
- JAK inhibitors.
- Topical corticosteroids and topical 5-aminosalicylic acid preparations.
- Cyclosporine and tacrolimus.
- Drugs that could interact with ABX464 should be avoided especially the CYP1A2 inducers/inhibitors. The following CYP1A2 inducers/inhibitors are prohibited during the whole course of the study (ciprofloxacin,

enoxacin, fluvoxamine, montelukast, phenytoin, rifampicin, ritonavir, teriflunomide). Please refer to Appendix #1.

The UGT1A9 inhibitors and OAT P1B1/P1B3 inhibitors/substrates that could interact with ABX464 and its metabolite ABX464-N-Glu should also be avoided. Please refer to Appendix #1.

- Use of any investigational or non-registered product within 3 months preceding Day 0 except ABX464.

7. SUBJECT COMPLETION AND WITHDRAWAL

7.1. Subject Completion

Treatment duration with ABX464 is 48 months or earlier if one study discontinuation criterion is met (defined below).

The subjects exiting the study must perform the Follow-up and End of Study (EoS) visits 4 weeks after last study drug intake. They will be then treated according to the standard of care upon study treatment interruption.

7.2. Study discontinuation criteria

Subjects who are not found eligible or not willing to enter the ABX464-108 study are not considered as prematurely discontinued as they have completed the scheduled treatment of ABX464-102 study.

A subject can be withdrawn at any time from the study for the following reasons:

Subject's study discontinuation could occur for the following reasons:

- Investigator's decision;
- An Adverse Event or an intercurrent condition that preclude continuation of treatment;
    - specifically, an increase ≥ 3.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or an increase ≥ 2.0 x ULN in Alkaline phosphatase or in total bilirubin requires close observation with repeating liver enzymes and serum bilirubin tests two times weekly and clinical investigation to understand the etiology of this elevation. Frequency of retesting can decrease to once a month if abnormality stabilizes after the initial two weeks of follow-up and if the patient is asymptomatic. Discontinuation of the study treatment should occur if:
        - ALT or AST > 8xULN
        - ALT or AST > 5xULN for more than 2 weeks
        - ALT or AST > 3xULN and total bilirubin > 2xULN or INR>1.5
        - ALT or AST > 3xULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%);
    - Severe (grade 3 or higher) infection, a severe (grade 3 or higher) opportunistic infection, or sepsis;
    - Any cardiac AESI or condition diagnosed during the course of the study and assessed by the clinical adjudication committee as changing the risk/benefit balance for the subject;
    - New onset of acute pancreatitis;
    - Malignancies (including non-melanoma skin cancers);
    - Any relevant toxicity or negative change in the risk/benefit assessment leading to an unacceptable risk for the subject or any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment. This may be applicable but is not limited to the following cases: occurrence of AEs which character, severity or frequency is new in comparison to the existing risk profile, or clinically significant abnormal laboratory results, including new onset anemia (defined as a hemoglobin decrease >2 g/dL from baseline or hemoglobin <8 g/dL
- Worsening of the UC defined as a 2-point increase in the pMMS, with pMMS ≥ 4 on 2 separate occasions 7 day-apart and confirmed by an endoscopy sub score of 2 points or higher; subject who would experience a treatment failure during the study may be withdrawn at any time. S/he will have to be treated according to standard of care as soon as s/he is discontinued from study treatment because of study withdrawal;
- Withdrawal of consent;
- Pregnancy;
- Patients included with a history of cardiac ischemic disease and/or congestive heart failure will be discontinued from the study, will perform the End of Study Visit 4 weeks after last study drug administration and will then be treated according to the standard of care upon study treatment interruption.
- Administrative reasons from Sponsor.

7.3. Study Discontinuation

All subjects, regardless of the completion or premature discontinuation, should perform the Follow-up and End of Study Visits according to the study flow-chart.

8. ADVERSE EVENTS (AE), ADVERSE EVENT OF SPECIAL INTEREST (AESI) AND SERIOUS ADVERSE EVENTS (SAE)

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

During the screening period, only adverse event related to the screening procedures will be collected.

Any disease progression will not be reported in the eCRF as an adverse event, but will be documented in the efficacy section.

8.1. Definition of an AE

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

An AE can therefore be any 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.

8.2. Definition of an AESI

The following events will be considered AESI and must be reported to Intuvigilance (same procedure as SAE).

Skin Lesions (regardless of its severity)

A dermatologist consultation should be scheduled to evaluate the type of lesion, its severity and etiology. An anonymized medical report shall be provided.

Headaches

Headaches are frequently reported by patients dosed with ABX464. Abivax follows closely, by means of individual adapted questionnaire, provided in Appendix #4, this AE in specific situations (i.e. headache lasting longer than 72 hours AND not resolved by standard painkillers).

Anemia

Some degree of anemia was found in the 9-month marmoset study with ABX464-N-Glu. Although it has not been reproduced clinically, Abivax performs surveillance for anemia by means of regular determination of hemoglobin and hematocrit levels. Anemia defined as Hb drop > 2 g/dL from baseline or Hb < 8g/dL will be reported as AESI.

Hepatic enzymes

ABX464 showed liver findings in some toxicological studies, hence attention is paid to identification of liver enzymes elevations in subjects. No human predictors of hepatoxicity for ABX464 or its metabolite, ABX464-N-Glu, have been identified. Based upon preclinical and clinical available data, a DILIsym evaluation of ABX464 was conducted and concluded that there was no risk of DILI in these patients. A signal detection analysis of ALT/AST changes in subjects treated with ABX464 did not reveal any meaningful variation of the mean ALT/AST measurement throughout treatment nor an increased incidence of any liver function tests (LFTs). Sporadic cases of isolated alkaline phosphatase increase have been reported in patients dosed with ABX464.

A specific liver function monitoring plan is implemented in all clinical studies (see Section 5.3.10 and Section 7.2) during the course of treatment and a measurement of LFTs 4 weeks after treatment interruption (during End of Study visit). The LFTs should, as per the clinical protocols, include at least the determination of the liver transaminases (ALT/AST), gamma-glutamyl transferase (GGT), alkaline phosphatase and total bilirubin. Specifically, an increase ≥ 3.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or an increase ≥ 2.0 x ULN in total bilirubin without initial findings of cholestasis (elevated alkaline phosphatase) will be reported as AESI.

Severe (grade ≥ 3) infections and opportunistic infections

Immunosuppression has been observed during the 9-month cynomolgus monkey study with ABX464-N-Glu dosed directly by oral gavage. Therefore, serious (grade 3) infections and opportunistic infections due to bacterial,

mycobacterial, invasive fungal, viral, or parasitic organisms (including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis) will be reported as AESIs. Subjects will be monitored for the development of signs and symptoms of infection during treatment with ABX464. ABX464 will be discontinued if a subject develops a severe (grade 3 or higher) infection, a severe (grade 3 or higher) opportunistic infection, or sepsis.

Acute pancreatic adverse events

Cases of transient increase in lipase serum levels have been observed in ABX464 clinical studies in ulcerative colitis patients as well as in patients with COVID-19 infection (blinded placebo/ABX464 treatment). Therefore, lipase and amylase will be monitored in the clinical studies. An elevation of serum lipase and/or amylase at least three times greater than the upper limit of normal will be reported as AESI and a workup for a diagnosis of pancreatitis will be performed according to the Atlanta criteria for the definition of acute pancreatitis.

Definition of diagnosis of acute pancreatitis [10]

The diagnosis of acute pancreatitis requires two of the following three features:

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back);
- Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and
- Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging or transabdominal ultrasonography.

If abdominal pain suggests strongly that acute pancreatitis is present, but the serum amylase and/or lipase activity is less than three times the upper limit of normal, as may be the case with delayed presentation, imaging will be required to confirm the diagnosis. The CECT will be planned and performed locally in that case.

If the diagnosis of acute pancreatitis is established by abdominal pain and by increases in the serum pancreatic enzyme activities, a CECT is not usually required for diagnosis in the emergency room or on admission to the hospital.

Malignancies including Non-Melanoma Skin Cancers

Despite a lack/paucity of reported events in non-clinical and clinical trials, a potential impact on both innate and adaptive immune responses and the novel mechanism of action, could be a concern with regards to malignancies, mainly in the long-term. Therefore, all malignancies including non-melanoma skin cancers will be reported as an AESI.

Cardiac Fibrosis:

Two cases of cardiac fibrosis, likely associated with the marmoset wasting syndrome [11] , have been observed in a 9-month study with marmoset monkeys exposed to high doses of ABX464-N-Glucuronide. These findings were considered to be spontaneous. A review of the safety database for ABX464 has revealed no changes in troponin level compared with placebo or any increased reporting of cardiovascular adverse events compared with placebo. However, the following cardiac monitoring will be performed in this study:

Additional cardiac Laboratory monitoring procedures will include:

1. Monitoring of AST, Troponin and creatinine phosphokinase (CPK) blood levels at each study visit, including baseline visit plus the End of Study Visit
2. Monitoring of N-terminal pro b-type natriuretic peptide (NT-proBNP) blood levels every 6 months plus at the End of Study Visit.

A relative change of more than 20% from baseline values in cardiac laboratory parameters will be reported as an AESI.

Two-dimensional echocardiography with local evaluation will be performed every 6 months.

An independent Cardiovascular Safety Committee (ICVSC) will evaluate cardiac AESIs, treatment emergent echocardiographic findings, and treatment emergent changes of cardiac safety biomarkers (as detailed above).

The following treatment emergent adverse events (TEAEs) will also be categorized as Cardiac AESI:

Under the Cardiac SOC:

- Aortic valve disease
- Asystole

- Atrial fibrillation
- Atrial flutter
- 3rd degree AV block (AV block complete)
- Cardiac arrest
- Chest pain – cardiac
- Heart failure
- Left ventricular systolic dysfunction
- Mitral valve disease
- Mobitz (type) II atrioventricular block (type 2, 2nd degree AV block)
- Myocardial infarction
- Myocarditis
- Pericardial effusion
- Pericardial tamponade
- Pericarditis
- Pulmonary valve disease
- Restrictive cardiomyopathy
- Right ventricular dysfunction
- Sick sinus syndrome
- Tricuspid valve disease
- Ventricular fibrillation
- Ventricular tachycardia

8.3. Definition of a SAE

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 subject 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 subject 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-subject 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 elective treatment of a pre-existing condition that did not worsen after informed consent was given is not considered an AE.

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 subject 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.

8.3.1. 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).

8.4. Events or Outcomes Qualifying as AEs or SAEs

8.4.1. 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 sections 8.1 and 8.2 respectively. 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 but do not worsen, will **not** be reported as AEs or SAEs. However, if these findings or assessments are judged by the investigator to be more severe than expected considering the subject's condition, then they may be reported as AEs or SAEs.

8.4.2. Pregnancy report

Subjects 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 subject or partner of a male subject, 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 IntuVigilance Limited (see contact details in section 8.4) within 24 hours after knowledge of a subject's or partner's pregnancy. The subject 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 normally end 6 to 8 weeks following the estimated delivery date but could last up to one year after the delivery.

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 8.5, Time Period, Frequency, and Method of Detecting AEs and SAEs. Pregnancy information is collected from the signing of Pregnancy Follow up Inform Consent or Pregnant Partner Informed Consent to the end of the pregnancy follow-up.

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

All AEs, AESIs and SAEs occurring from the time a subject consent to participate in the study until 4 weeks after he or she has completed or discontinued the investigational product must be recorded in the subject's eCRF.

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

Hotline phone: +44 800 689 4129
Email Address: safety@intuvigilance.com

Fax number: +44 800 915 6753

Legislative guidance requires also reporting any **related** SAEs to be reported after the subject 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 4.0.

Subjects 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 subject'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 subject;
- 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;
- 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;
- Subject'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 subject, the same AE occurs on several occasions, the AE in question must be documented and assessed anew each time.

8.7. Reporting of AESIs and SAEs to ABIVAX or its designee

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

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

The SAE/AESI forms or paper report forms should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. 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/AESI, 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 product. It is therefore important that the investigator notifies promptly ABIVAX or designee of any SAE, in order for legal obligations and ethical responsibilities towards other subjects 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 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

An interim analysis was performed at M12.

The study analysis will be performed following database lock upon the completion of the last subject or upon its early discontinuation whichever occurs first.

9.1.1. Protocol deviations

Protocol deviations will be reviewed and classed as critical (immediate impact on patient safety or data integrity), major or minor during the data-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 subjects 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 subjects 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 subjects of the FAS population without any major protocol deviation.

9.1.3. Subjects/Subjects disposition

The number and the percentages of subjects enrolled will be tabulated. The reason for subject exclusions from each of the populations will also be listed. In addition, the number of discontinued subjects 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 doses will be presented on the FAS population.

9.2. Efficacy Analysis

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

Descriptive statistics will be presented by treatment arm and include:

- Quantitative variables: mean, standard deviation, minimum and maximum, 95% confidence intervals, median and quartiles will be presented when considered relevant. Number of filled and missing values will also be presented.
- Qualitative variables: count, percentage for each modality and 95% confidence intervals when relevant. Number of missing values will also be presented.

9.3. 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 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 the last dosing day;
- Any adverse event which occurs after the last dosing day.

Adverse events will be described by primary system organ class and preferred term. Numbers and percentage of subjects, 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
- TEAE of special interest

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 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].

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

9.3.1. Clinical laboratory evaluation

Descriptive statistics for laboratory parameters will be computed at each scheduled assessment. If relevant for some parameter, change from baseline will also be tabulated. In addition, shift tables from baseline will be presented.

9.4. Determination of Sample Size

Not applicable

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 / SIMBEC-ORION 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. For the containment and countering against the spread of the COVID-19 virus (coronavirus disease 19), alternative delivery methods of the medicinal product(s) (IMP) from the Hospital Pharmacy to trial subjects may be arranged to guarantee the access to the IMP and the treatment continuity to the subjects; for example, by using couriers dedicated to delivering to the subject's home or by delivering the medicinal product(s) to the caregiver/family members or delegates of the subject, if going to the clinical site is considered impossible or high risk for the subject. If a specialized courier is used for the transport of the medicinal product to the subject's home, the use of personal data will be guaranteed according to the applicable regulations on Privacy. Suitable remote communication mechanisms with the trial subjects will be guaranteed and adequate documentation of the procedures put in place will be maintained and described in the appropriate procedure and documented in subjects' medical source and Investigators' Site Files.
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
- EU Regulation 536/2014 of the European Parliament and of council, which introduces the Clinical Trials Information System (CTIS) that harmonizes the submission, assessment and supervision processes for clinical trials throughout Europe

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 subject 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. Subject Informed Consent

It is the responsibility of the investigator to give each subject full and adequate verbal and written information regarding the aims, methods, anticipated benefits and potential hazards. The subject 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 subject 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 subject's rights. Written consent (signed and dated by the subject and the investigator) must be obtained prior to admission. The subject must be provided with a copy of the subject information and informed consent.

The Investigator will be responsible for obtaining an ICF signed by the subject in accordance with ICH GCP guidelines to collect pregnancy information on any woman patient or partner of a male patient, who becomes pregnant while participating in this study.

The data collected in this study will be processed anonymously at ABIVAX. Subjects should be informed about the purpose of the planned computer data processing and the publication of the data (e.g. at scientific meetings). The subject must give consent to the computer processing and to the publishing of anonymous data.

The subject 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 Subjects

Insurance coverage will be provided for all subjects enrolled in the study from the time of the subject'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,…) subjects 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 subject'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 a "*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 subject 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. Study Monitoring

The study will be conducted in accordance with the ICH Note for Guidance on GCP (ICH, Topic 6, 1996). 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. For the containment and countering against the spread of the COVID-19 virus (coronavirus disease 19), remote subjects visit and remote monitoring methods may be implemented, including the ability to phone or video call the trial site staff, for the purpose of source data verification. These methods will be described in the appropriate procedure and documented in subjects' medical source and Investigators' Site Files.

During the monitoring visits, the monitor will:

- Ensure that the safety and the rights of subjects 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 ICH GCP guidelines, monitoring will include verification of data entered in the CRF against the original subject 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.

11.5. 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 GCP E6 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.

11.6. 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 subjects;
- 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.

11.7. Study and Site Closure

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

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.

11.8. 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 subjects, 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 subjects enrolled as well as contribution to the study conduct and preparation of final manuscript.

11.9. Ownership and Confidentiality

All information provided by ABIVAX and all data and information generated by the sites, as parts of the study (excluding the subjects' 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

Appendix 1: CYPIA2 inducers/inhibitors, OATB1B1/1B3 inhibitors and substrates, UGT1A9 inhibitors

CYP1A2 inducers/inhibitors (in bold: prohibited concomitant medications)

Inhibitors:

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

Inducers:

Montelukast, Phenytoin, Rifampicin, Ritonavir, Teriflunomide

OATB1B1/1B3 inhibitors and substrates (prohibited concomitant medications)

Substrates:

Asunaprevir, Atorvastatin, Atrasentan, Bosentan, Caspofungin, Cerivastatin, Daprevir, Docetaxel, Eluxadoline, Empagliflozin, Erythromycin, Fexofenadine, Fimasartan, Fluvastatin, Glecaprevir, Glyburide, Grazoprevir, Letermovir, Lopinavir, Lovastatin, Nateglinide, Nelfinavir, Olmesartan, Paritaprevir, Pitavastatin, Pravastatin, Repaglinide, Rosuvastatin, Simvastatin, Telmisartan, Torsemide, Voxilaprevir

Inhibitors:

Cyclosporine, Eltrombopag, Lapatinib, Lopinavir, Rifampicin, Ritonavir

UGT1A9 inhibitors (prohibited concomitant medications)

Inhibitors:

Regorafenib, Fosphenytoin, Phenytoin, Eltrombopag, Mefenamic acid, Diflunisal, Niflumic acid, Sorafenib, Isavuconazole, Deferasirox, Morniflumat, Rifampicin

Appendix 2 : SF-36 Questionnaire (English Version)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activitie
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your norma work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 3: Mayo Score (Ulcerative Colitis)

Components of the Mayo Score	
Stool frequency	
0	Normal
1	1–2 stools/day more than normal
2	3–4 stools/day more than normal
3	5 or more stools/day more than normal
Rectal bleeding	
0	None
1	Visible blood with stool less than half the time
2	Visible blood with stool half of the time or more
3	Passing blood alone
Mucosal appearance at endoscopy	
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity	
0	Normal
1	Mild
2	Moderate
3	Severe

Appendix 4: Follow-up Headache questionnaire

Subject ID: _____ **DOB:** _____ **Date:** _____

Please describe your headaches:

1. How long after taking the study medication does your headache start?

◯ within 30 minutes ◯ within 60 minutes ◯ 1-2 hours ◯ 3-4 hours ◯ > 4 hours

2. How frequent are your headaches?

◯ less than 1 per day ◯ once or twice a day ◯ 3 times a day ◯ >3 times per day

3. How long do your headaches last in days?

◯ less than a day ◯ 1 day ◯ 2 days ◯ 3 days ◯ 4 days ◯ 5 days ◯ 6 days ◯ 7 days ◯ >7 days

4. How severe are your headaches? (*on a scale of 0-10 with 10 being the most severe*) ◯ On average my headache would be a #_____ ◯ My most severe headache would be a #_____

5. Do you have more than one type of headache? ◯ Yes ◯ No

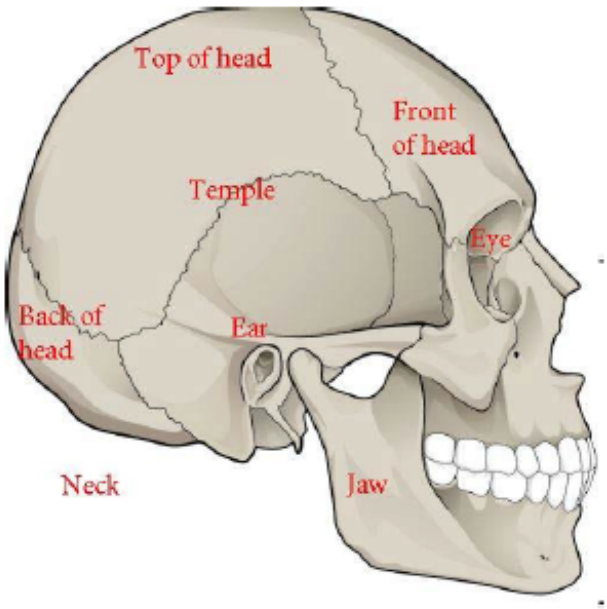
**If YES to above, please focus the following questions on your worst disability headache type*

6. Using the image below as a guide, please check where your headaches are generally located (*circle left and/or right when indicated*)

◯ Temple (R L) ◯ Back of head ◯ Front of head ◯ Ear (R L)

◯ Top of head (R L) ◯ Eye (R L) ◯ Neck ◯ Jaw

◯ Around head ◯ Other _____



7. Your headaches are worse in the:				
◯ morning	◯ afternoon	◯ evening	◯ during the night	◯ no pattern

8. Are your headaches worse lying down or standing?	◯ Lying down	◯ Standing

9. Do your headaches wake you up in the middle of the night?	◯ Yes	◯ No	If yes, how often:_____?

10. Headache relief from medication: Do you take any medication to treat your headaches? If yes, Please, include all Over-The-Counter and Prescription medications you are using to treat your headaches:

Medication Name & dose	Average & Maximum used in 1 day	How many times weekly?

11.

11. Headache relief: ◯ without medication

After medication intake: ◯ within 1 hour ◯ 1-2 hours ◯ > 2 hours ◯ never became pain free after medication.

Duration of treatment: ◯ ≤ 1 day ◯ a few days < 1 week ◯ > 1 week ◯ never became pain free

12. Do you have other symptoms during your headache?

**mark all that apply*

◯ nausea or upset stomach/ vomiting	◯ sensitivity to smells	◯ Sensitivity to light (prefer a dark room)
◯ Difficulty thinking/concentrating/focus	◯ Sensitivity to sound (prefer a quiet room)	◯ Difficulty speaking/slurred speech
◯ Sore/stiff neck	◯ Increased urination	◯ Vision changes (blurred, spots, patterns)
◯ Anxiety	◯ Eye tearing in only ONE EYE	◯ Irritability
◯ Runny nose in only ONE NOSTRIL	◯ Memory problems	◯ Ringing in ears
◯ Increased appetite	◯ Decreased appetite	◯ Eye redness (R L Both)
◯ Drooping eyelid (R L Both)	◯ Diarrhea	◯ Swelling of eyelid (R L Both)
◯ Constipation	◯ Change in pupil (larger smaller)	◯ Insomnia
◯ Dizziness (lightheaded, woozy)	◯ Vertigo (the room appears to spin)	◯ Sleepiness
◯ Numbness/tingling (R L Both)	◯ Confusion	◯ Facial droop, droopy eyelid, unable to move one arm or leg
◯ Imbalance		

13. Do you have any of the following symptoms before your headache begins: (**check all that apply)*

◯ Flashing lights	◯ Loss of vision in one eye	◯ Tunnel vision	◯ Spots: bright/dark
◯ Zigzag lines	◯ Loss of vision on one side	◯ Double vision	◯ Geometric forms
◯ Wavy lines	◯ Total blindness	◯ Distorted vision	◯ Numbness/tingling (R L Both)
◯ Speech difficulty	◯ Vertigo	◯ Dizziness/unsteadiness	◯ Light-headedness
◯ One-sided weakness (R L Both)	◯ Confusion / déjà vu / hallucinations	◯ Other: _____	