CLINICAL STUDY PROTOCOL
ABX464-104

Sponsor:	ABIVAX 5, rue de la Baume 75008 Paris FRANCE
Investigational product:	ABX464
Product code:	ABX464
INN:	Obefazimod
Therapeutic indication:	Moderate to severe ulcerative colitis
Study code:	ABX464-104
EudraCT number:	2019-000733-39
IND number:	141396
Protocol title:	A phase 2b, open-label, efficacy and safety study of ABX464 as maintenance therapy in patients with moderate to severe Ulcerative Colitis.
Version number:	5.1
Version date:	July 11th, 2022

CLINICAL STUDY PROTOCOL VALIDATION PAGE

Study code	ABX464-104
EU CT number	2019-000733-39
IND number	141396
Detailed Title	A phase 2b, open-label, efficacy and safety study of ABX464 as maintenance therapy in patients with moderate to severe Ulcerative Colitis.
Document date & version	July 11th, 2022/ Final Version 5.1
Validation	Sophie BIGUENET (CMO): Date:
	Paul GINESTE (VP, Clin Ops): Date:
	Mary MANTOCK (VP, Regulatory Affairs) Date:

CLINICAL STUDY PROTOCOL

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Detailed Title	A phase 2b, open-label, efficacy and safety study of ABX464 as maintenance therapy in patients with moderate to severe Ulcerative Colitis.
Study Phase	Phase 2b
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Date/Version	July 11th, 2022 / Version 5.1

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INVESTIGATOR AGREEMENT PAGE

EudraCT number 2019-000733-39

IND number 141396

Detailed Title: A phase 2b, open-label, efficacy and safety study of ABX464 as maintenance therapy in patients with moderate to severe 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 patients is jeopardized.
- To conduct the study in accordance with the ICH GCP (R2) guidelines, US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations), the European Union Clinical Trials Directive 2005/28/EC, EudraLex GMP guidelines Annex 13, the provisions of the Helsinki Declaration, the EU Regulation 536/2014 of the European Parliament and of council, the EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and relevant legislation in force.
- I am thoroughly aware of the study drug specifications and adverse events as described in the protocol and the current Investigator's Brochure and any other information provided by the Sponsor.
- To ensure that sub-investigator(s) and other relevant members of my staff involved in the study are fully aware of their responsibilities regarding this study and will conduct the study according to the protocol.

Investigator's Name: _____

Investigator's Signature: _____

Date: _____

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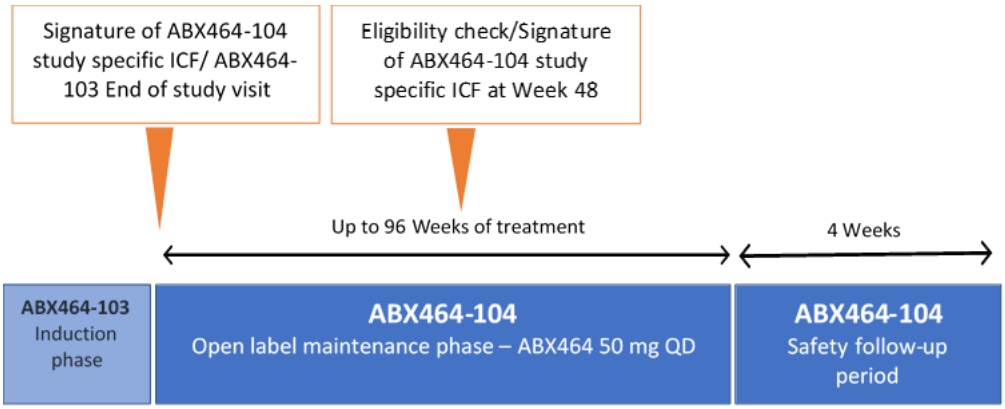
ABBREVIATIONS

Abbreviation or Term	Definition
ABX	Abivax
ABX464-N-Glu	ABX464-N-Glucoronide (ABX464 main metabolite)
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
AUC0-24	area under the plasma concentration-versus-time curve from zero to 24 hours
AUC0-∞	area under the plasma concentration-versus-time curve from zero to infinity
AUC0-t	area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration
BMI	Body Mass Index
BOLS	Baseline of the Open Label Study
CBC	Cap Binding Complex
CI	Confidence Interval
Cmax	peak plasma concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CPK	Créatine PhosphoKinase
CRF	Case Report Form
CRP	C-Reactive Protein
CTC-AE	Common Terminology Criteria for Adverse Events, version 5.0
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome
DBP	Diastolic Blood Pressure
DSS	Dextran sulfate sodium
DSMB	Data and Safety Monitoring Board
ECCO	European Crohn's and Colitis Organization
ECG	Electrocardiogram
EDTA	ethylenediaminetetraacetic acid
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GHAS	Global Histological Assessment Score
GLDH	Glutamate Dehydrogenase
GLS	Global Longitudinal Strain
GM	Geometric Mean
H	Hours
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HR	heart rate
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonization
ICVSC	Independent Cardiovascular Safety Committee
IEC	Independent Ethics Committee
IL-1b	Interleukine 1b
IL-6	Interleukine 6
IL10	Interleukine 10
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISB	Induction study baseline
JAK	Janus Kinase
LFTs	Liver Function tests
LVEF	Left Ventricular Ejection Fraction
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities (version 22.0)
mg	Milligram
MH	Mucosal Healing
Min	Minimum
miR	micro-RNA
mL	Milliliter
mmHg	millimeters of mercury
MMS	Modified Mayo Score
NOAEL	No Observed Adverse Effect Level
NT-proBNP	N-terminal pro-brain natriuretic peptide
pMMS	partial Modified Mayo Score
PT	Preferred Term
QD	*Quaque Die (Latin)* ; Once daily
QoL	Quality of Life
QTc	heart-rate–corrected QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) using Bazett's formula
R	Accumulation ratio
RHI	Robarts Histopathology Index
RNA	Ribonucleic Acid
RV	Right Ventricle
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SES-CD	Simple Endoscopic Score for Crohn's Disease
SOC	system organ class
t1/2	terminal half-life
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to peak plasma concentration
TMS	Total Mayo Score
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
ULN	Upper Limit Normal
Vd/F	Volume of Distribution
vs.	Versus
W	Week

Synopsis

Study n°	ABX464-104	**Clinical Phase**	2b
		Type of Study	Maintenance therapy in patients with moderate to severe UC
Study title	A phase 2b, open-label, efficacy and safety study of ABX464 as maintenance therapy in patients with moderate to severe Ulcerative Colitis.		
Investigators and study centers	Sixty-nine sites in Europe and in Canada will participate in this study.		
Study Duration	Recruitment period: Q4 2019 – Q2 2021 Overall Study period: Q4 2019 – Q4 2023		
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 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 (QD) at 50 mg in patients with moderate to severe ulcerative colitis (UC) who have been previously enrolled in the ABX464-103 clinical study (induction study) and who are willing to receive their treatment with ABX464 as long-term (maintenance) therapy of remission. All patients who have completed the 16-week (± 4 days) induction treatment period (ABX464-103) will be eligible for this maintenance study regardless of their clinical response and will receive 1 capsule of ABX464 50mg once daily during up to 96 weeks providing the patient has a clinical response at week 48.  The study design is presented below: Patients will be treated for a maximum of 96 weeks in this maintenance study. After the treatment period, patients will be followed for 4 additional weeks for safety purposes. Alternatively, eligible subjects willing to continue study treatment will be offered to take part in a long term follow up safety study (ABX464-108) at the end of treatment (ie Week 96). ABX464-108 study is a separate clinical study requiring health authorities and ethics committees' approvals. From Day 1 onwards, patients will be seen at the investigational site every 4 weeks up to week 48 and then quarterly until weeks 96. Flexible sigmoidoscopy with rectal and/or sigmoidal biopsies will be performed, for all patients at week 48 and at week 96. Additional flexible sigmoidoscopies may be performed during the open label phase based on medical judgement. During the open label maintenance phase, in the event of clinical progression of the disease, defined as at least a 2-point increase from the screening partial Modified Mayo Score (pMMS) with a pMMS ≥ 4 confirmed by an endoscopy sub score of 2 points or higher, the patient will exit the study. .		

Study n° ABX464-104	**Clinical Phase** 2b **Type of Study** Maintenance therapy in patients with moderate to severe UC
Study Objectives	**Primary Objective** The primary objective of the study is to assess in all patients the long-term efficacy of ABX464 given at 50 mg QD on clinical remission at week 48 compared to the induction study (ABX464-103) baseline (ISB). **Secondary Objectives** *Week 24 and 48 secondary objectives are:* ▪ To evaluate clinical remission at week 48 compared to the baseline of the open label study (BOLS). For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, the clinical remission at week 48 will be compared to week 8 of the induction study. ▪ To evaluate the effect of ABX464 50 mg QD on Modified Mayo Score (MMS) at week 48 and on partial Modified Mayo Score (pMMS), among all patients, at every study visit compared to ISB. ▪ To evaluate the effect of ABX464 50 mg QD on endoscopic improvement and remission and sustained endoscopic improvement and remission, by segment at week 48 compared to ISB and BOLS. For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, endoscopic improvement at week 48 will be compared to week 8 of the induction study. ▪ To evaluate the proportion of patients with glucocorticoid-free clinical remission at week 48. ▪ To evaluate the effect of ABX464 50 mg QD on stool and rectal bleeding frequency at every study visit compared to BOLS. ▪ To evaluate the effect of ABX464 50 mg QD on fecal calprotectin and CRP levels at week 24 and week 48 visits compared to BOLS. ▪ To evaluate the effect of ABX464 50 mg QD on clinical response at week 48 compared to ISB and BOLS. For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, endoscopic measurements at week 48 will be compared to week 8 of the induction study. ▪ To evaluate the effect of ABX464 50 mg QD on miR-124 expression in colon tissue (RNA later) at week 48 and in total blood at week 24 and week 48. ▪ To evaluate the effect of ABX464 50 mg QD on patients' quality of Life (QoL) measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at week 24 and week 48 compared to BOLS. ▪ To evaluate the effect of ABX464 50 mg QD on the rectal/sigmoidal infiltrates using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at week 48 compared to ISB and BOLS. For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, endoscopic measurements at week 48 will be compared to week 8 of the induction study. ▪ To evaluate the long-term safety profile of ABX464 50 mg QD. *Week 96 secondary objectives are:* ▪ To evaluate the effect of ABX464 50 mg QD on partial Modified Mayo Score (pMMS) at every study visit (week 48 to 96) compared to ISB and on Modified Mayo Score at week 96. ▪ To evaluate the effect of ABX464 50 mg QD on stool and rectal bleeding frequency at every study visit (week 48 to 96) compared to BOLS. ▪ To evaluate the effect of ABX464 50 mg QD on fecal calprotectin and CRP levels at week 60, 72, 84 and week 96 visits compared to BOLS. ▪ To evaluate the effect of ABX464 50 mg QD on miR-124 expression in colon tissue (RNA later) and in total blood at week 96. ▪ To evaluate the long-term safety profile of ABX464 50 mg QD. *The echocardiography objective is:* ▪ To evaluate the effect of ABX464 on cardiac function as assessed through echocardiograms.
Study Endpoints	**Primary Endpoint:** Proportion of patients with clinical remission at week 48 compared to induction study baseline. Clinical remission, based on the Mayo Scoring system, is defined as stool frequency sub score = 0 or 1 and rectal Bleeding sub score = 0 and endoscopy sub score = 0 or 1 (modified to exclude friability). **Secondary Endpoints:** *The week 24 and 48 secondary endpoints are:*

Study n° ABX464-104	**Clinical Phase** 2b **Type of Study** Maintenance therapy in patients with moderate to severe UC

- Reduction relative to baseline in Modified Mayo Score at week 48 and in partial Modified Mayo Score at every study visit among all patients.
- Proportion of patients with either endoscopic improvement or/and endoscopic remission by segment at week 48 among all patients.

Endoscopic improvement is defined as a Mayo endoscopic sub score of ≤1 (excluding friability)

Endoscopic remission is defined as a Mayo endoscopic sub score of 0.

- Proportion of patients with sustained endoscopic improvement or/and sustained endoscopic remission at week 48.

Sustained endoscopic improvement is defined as the number of patients with endoscopic improvement at week 48 among patients who had endoscopic improvement during the Induction study (at week 8 or week 16). Sustained endoscopic remission is defined as the number of patients with endoscopic remission at week 48 among patients who had endoscopic remission during the Induction study (at week 8 or week 16).

- Proportion of patients with glucocorticoid-free clinical remission at week 48.

Glucocorticoid-free clinical remission is defined as clinical remission in addition to not requiring any treatment with glucocorticoids for at least 8 weeks prior to week 48.

- Reduction relative to baseline in stool and rectal bleeding frequency at every study visit.
- Reduction relative to baseline in fecal calprotectin and CRP levels at week 24 and 48.
- Proportion of patients with clinical response at week 48. Clinical response is defined as: a reduction in Modified Mayo Score ≥ 2 points and ≥ 30 % from baseline with an accompanying decrease in rectal bleeding sub-score ≥ 1 point or absolute rectal bleeding sub-score ≤ 1 point.
- Change relative to baseline in miRNA-124 expression in rectal/sigmoidal biopsies at week 48 and in total blood at week 24 and week 48.
- Scores and changes from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) domains at week 24 and 48.
- Reduction relative to ISB of infiltrate/histopathology (rectal/sigmoidal biopsies) using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at week 48.

The week 96 secondary endpoints are:

- Reduction relative to baseline in Modified Mayo Score at week 96 and in partial Modified Mayo Score at every study visit (week 48 to 96) among all patients.
- Proportion of patients with either endoscopic improvement or/and endoscopic remission by segment at week 96.
- Proportion of patients with sustained endoscopic improvement or/and sustained endoscopic remission at week 96.
- Reduction relative to baseline in stool and rectal bleeding frequency at every study visit (week 48 to 96).
- Reduction relative to baseline in fecal calprotectin and CRP levels at week 60, 72, 84 and 96.
- Proportion of patients with clinical response at week 96.
- Change relative to baseline in miRNA-124 expression in rectal/sigmoidal biopsies and in total blood at week 96.

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 from-previous echocardiogram in Global Longitudinal Strain (GLS).
- Number of subjects with a relative percentage reduction in GLS by > 15% from the previous echocardiogram.
- 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.

Study n° ABX464-104	**Clinical Phase** 2b **Type of Study** Maintenance therapy in patients with moderate to severe UC
	Safety endpoints: ▪ Number and rate of all adverse events, causally related adverse events, all SAE, and causally related SAEs classified by severity. ▪ Incidence of treatment-emergent serious adverse event, hospitalizations, total inpatient days. ▪ Incidence of adverse events leading to investigational product discontinuation. ▪ Number of clinically significant laboratory abnormalities.
Main Selection Criteria	**Inclusion criteria:** **A patient will be eligible to participate in this study if ALL the following criteria are met:** ▪ Patients must have completed the 16-week (± 4 days) induction treatment period (ABX464-103). ▪ Patients are able and willing to comply with study visits and procedures as per protocol. ▪ Patients should understand, sign and date the written voluntary informed consent form prior to any protocol-specific procedures are performed. ▪ Patients should be affiliated to a social security regimen (for French sites only). ▪ Females and males receiving the study treatment (potentially in combination with immunosuppressant) and their partners must agree to use a highly effective contraceptive method during the study and for 6 months (180 days) after end of study or early termination. Contraception should be in place at least 2 weeks prior to screening. Women must be surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) or in the postmenopausal state (no menses for 12 months without an alternative medical cause) or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (WOCBP) will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception aiming at inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the patient. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle. Female and male patients must not be planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male patients should use condom during the trial and for 6 months (180 days) post completion of their participation in the study. Male patients must not donate sperm as long as contraception is required. *Criteria that should be met by patients at week 48 to be eligible for 48 additional weeks of study treatment.* ▪ Patients should be in clinical response. Clinical response is defined as: a reduction in Modified Mayo Score ≥ 2 points and ≥ 30 % from baseline (induction) with an accompanying decrease in rectal bleeding sub-score ≥ 1 point or absolute rectal bleeding sub-score ≤ 1 point. ▪ Patients able and willing to continue the study treatment and who are compliant with study visits and procedures and who signed the update of the written voluntary informed consent. **Exclusion Criteria:** **Patients who meet any of the following exclusion criteria will be excluded from the study:** ▪ Patients who permanently discontinued study treatment in induction study (ABX464-103) because of an adverse event (AE) regardless of relatedness to investigational product. ▪ Patients who have developed any major illness/condition or evidence of an unstable clinical condition (except UC) that, in the investigator's judgment, will substantially increase the risk to the participant if he or she participates in the study. ▪ Patients with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. ▪ Patients who are participating or plan to participate in other investigational studies (other than induction study) during the study.
Medications and Corticosteroids Tapering	**Allowed Concomitant Medications:** ▪ Oral 5-aminosalicylic acid at stable dose. ▪ Immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate at stable dose.

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	▪ Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) at stable dose. ▪ For patients on oral corticosteroids at baseline, prednisone or prednisone equivalent ≤20 mg/day; beclomethasone diproprionate (≤5mg/day) or budesonide MMX (≤9 mg/day). **Tapering period:** For patients on oral corticosteroids at baseline, a tapering of steroids should be performed from baseline onwards. The rate of prednisone or prednisone equivalent tapering should not exceed 5 mg/week till complete discontinuation. The tapering can be stopped at any time based on medical judgment. No further oral corticosteroids dose escalation is allowed. **Prohibited Concomitant Medications:** ▪ Tumor necrosis factor [TNF] inhibitors, vedolizumab or others biologic therapies. ▪ JAK inhibitors. ▪ Topical corticosteroids and topical 5-aminosalicylic acid preparations. ▪ Cyclosporine and tacrolimus. ▪ Vaccination with live components during the study and up to 8 Weeks after the last dosing (COVID 19 Vaccine is allowed). ▪ Drugs that inhibit or induce CYP1A2 (cf. Appendix #1). ▪ Drugs that inhibit UDP-glucuronosyltransferase (UGT) IA9 activity and inhibitors or substrates of organic anion transporter (OAT) P1B1/P1B3 transporters (cf. Appendix #1). ▪ Use of any investigational or non-registered product.
Premature trial discontinuation	Subjects who are not found eligible for the second year of treatment are not considered as prematurely discontinued as they have completed the first-year treatment. Patient's premature trial discontinuation could occur for the following reasons: ▪ Investigator's decision: 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. ▪ An Adverse Event or an intercurrent condition that preclude continuation of treatment; Specifically, o 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 this 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%). o A severe (grade 3 or higher) infection, a severe (grade 3 or higher) opportunistic infection, or sepsis. ▪ 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. ▪ Withdrawal of consent. ▪ Pregnancy. ▪ 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 study subjects. ▪ New onset of acute pancreatitis. ▪ Malignancies (including non-melanoma skin cancers). ▪ Medically significant abnormal laboratory results, including new onset anemia (defined as a hemoglobin decrease >2 g/dL from baseline or hemoglobin <8 g/dL) - note: transient abnormal values, and/or abnormal values related to an existing condition that doesn't constitute a worsening will not be a criteria for discontinuation.

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	▪ 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 ▪ 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.
Data Safety Monitoring Board (DSMB) – Independent Cardiovascular Safety Committee (ICVSC)	A Data and Safety Monitoring Board (DSMB) with expertise and experience in the management in UC will review the safety of the trial every 2 months during the entire study period. In addition, DSMB will be review all potential causally related serious adverse events (SAE) within 7 days of the initial report. 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	This study is an open label extension study. Sample size calculation is therefore not applicable.
Statistical Methods	**Efficacy Analysis** Descriptive statistics will be presented for all efficacy variables for each measurement timepoint. In addition, subgroup descriptive analysis will be performed according to the patient status at the end of the induction study (clinical remission, clinical response, or no clinical response), and the treatment received during the induction phase (ABX464 25 mg, 50 mg or 100 mg, or matching placebo). **Interim analysis:** An interim analysis will be performed when all the subjects reach W48 visit. The interim analysis will include efficacy and safety data such as the following: ▪ Reduction relative to baseline in Modified Mayo Score and in partial Modified Mayo Score at every study visit among all patients. ▪ Clinical response and remission, endoscopy improvement and remission. ▪ Glucocorticoid-free clinical remission at week 48. ▪ Fecal calprotectin results. ▪ Safety parameters. ▪ Hematology and biochemistry parameters. **Safety Analysis** Adverse events will be coded using the standard dictionary (most recent MedDRA version) down to the lower-level term (LLT). Analysis of safety will be performed on the safety data set consisting of all patients who received at least one dose of ABX464 in the study. The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the "CTC-AE" (Version 5.0) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values. Adverse events will be tabulated (counts and percentages). 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. Frequency and percentage of patients and number of occurrences of adverse events will also be presented for serious TEAEs, TEAEs leading to study drug discontinuation, discontinuation from the study or death and TEAEs of special interest Clinical laboratory parameters, including echocardiography parameters and vital signs, will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Frequency and percentage of patients with normal, abnormal and abnormal clinically significant ECG results will also be summarized. The number of patients with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables.

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 patients

Patients may live with a considerable symptom burden despite medical treatment (66% describe interference with work and 73% with leisure activities) [1].

Although most patients present with mild-to-moderate UC, 10% of patients initially present with severe disease. Additionally, approximately 15% of patients 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 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].

Patients 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 patients 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 patients with acute severe ulcerative colitis will respond to a short course of intravenous corticosteroids, up to a third will fail to improve. In these patients with steroid-refractory colitis, the choice is between rescue medical therapy with ciclosporin, anti-TNF Alpha, vedolizumab, JAK inhibitors or surgery. Anti-tumor necrosis factor (TNF) therapy is effective for the treatment of ulcerative colitis (UC).

Nevertheless, up to 30% of patients show no clinical benefit despite optimal treatment, while another 40% of patients 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

The chemical name of ABX464 molecule is 8-chloro-N-[4-(trifluoromethoxy) phenyl]quinolin-2-amine, or (8-chloro-quinolin-2-yl)-(4-trifluoromethoxy-phenyl)-amine. Its molecular weight is 338.7 g/mol. The study drug is formulated as hard gelatin, powder-filled capsules (size 1).

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 blood and rectal biopsies of patients treated with ABX464 in the phase 2b trial (UC)

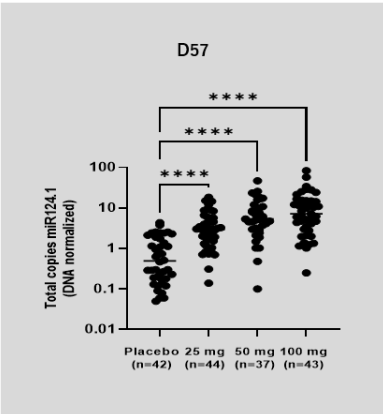
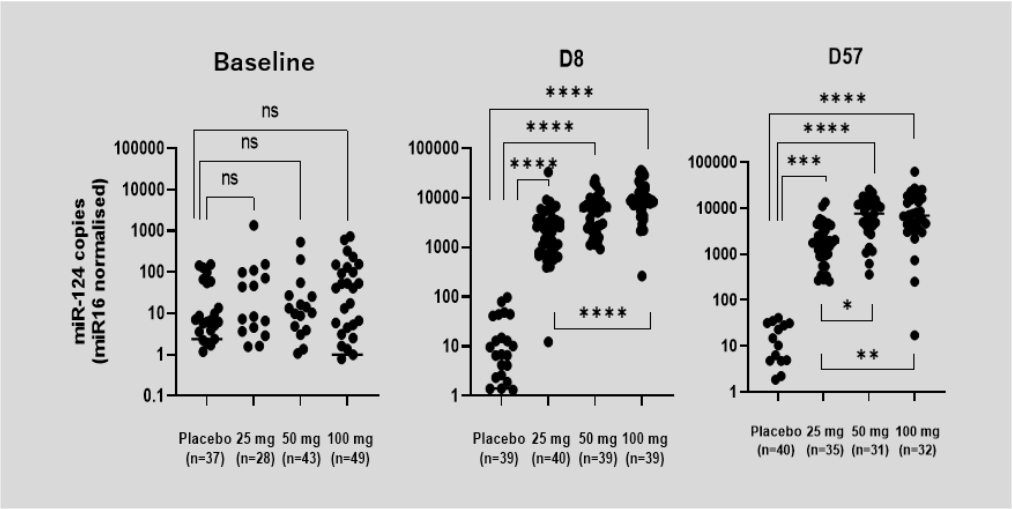


Figure 2 : MiR 124 induction in blood of patients treated with ABX464 in the phase 2b trial (UC)



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.

In vivo evidence for the role of ABX464 in inflammation

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 [10]. 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 [11]. 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

The toxicity of ABX464 and ABX464-N-Glu was studied in a range of rodent and non-rodent species (rats, rabbits, dogs, cynomolgus and marmoset monkeys, and minipigs) 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.

Reproductive toxicity

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 subjects 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's 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), in COVID-19 infected patients (ABX464-401) and in Japanese Healthy Volunteers (ABX464-921).
- Ongoing 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.

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 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 240 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 at 95 study sites in 15 European countries, Canada and the US. It had three once-daily oral ABX464 treatment groups (25mg, 50mg and 100mg) and one placebo group. A total of 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 tumour 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 1 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)	All patients	-1027.7	-2192.8 **	-2316.8 **	-2280.9 **

Mean change from baseline
**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

Overall, the safety profile of ABX464 appears to be safe and well tolerated. The most frequently reported adverse events (AEs) were headache, nausea, vomiting, abdominal pain, back pain, and diarrhea which were mostly of mild to moderate intensity, occurring after treatment onset and transient in nature.

A dose relationship in the occurrence of these AEs was observed, especially with respect to headache.

No signs of hepatotoxicity have been observed in any of the subjects treated with ABX464 in the previously conducted or ongoing clinical trials. ABIVAX and its clinical experts consider that subjects treated with ABX464 are not at increased risk of developing drug-induced hepatotoxicity. A specific liver function monitoring plan has been implemented in the present clinical study (see Section 7.2).

Altogether, ABX464 efficacy and safety results in nonclinical models of inflammation and in subjects with IBD warrant the continuation of the clinical development of ABX464 in IBD. For further information regarding the nonclinical and clinical data for ABX464, refer to the current Investigator's Brochure.

1.3. Rationale for the clinical study and study design

A Phase 2a 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 Ulcerative Colitis 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%).
- Endoscopic improvement rate of 50.0 %* (p=0.03) of ABX464 patients (Placebo = 11.1%).
- Clinical Response rate of 70.0 % of ABX464 patients (Placebo = 33.3%).

No severe or serious adverse reactions reported. Most adverse events were of mild to moderate intensity.

At the end of the completed 2-month induction study, 22 patients (15 previously treated with ABX464 and 7 who had received placebo) opted to enroll in the 12-month open-label maintenance study, ABX464-102. At month 9, 19 of the 22 patients were still in the study, receiving a once-daily, oral capsule of 50mg ABX464. This interim analysis showed that ABX464 continued to have a good efficacy and safety profile when administered chronically.

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 during12 months treatment.

All patients who had an endoscopy performed, had an endoscopic subscore 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. These efficacy and safety results 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 assess in all patients the long-term efficacy of ABX464 given at 50 mg QD on clinical remission at week 48 compared to the induction study (ABX464-103) baseline (ISB).

2.2. Secondary Objectives

Week 24 and 48 secondary objectives are:

- To evaluate clinical remission at week 48 compared to the baseline of the open label study (BOLS). For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, the clinical remission at week 48 will be compared to week 8 of the induction study.
- To evaluate the effect of ABX464 50 mg QD on Modified Mayo Score (MMS) at week 48 and on partial Modified Mayo Score (pMMS), among all patients, at every study visit compared to ISB.
- To evaluate the effect of ABX464 50 mg QD on endoscopic improvement and remission and sustained endoscopic improvement and remission, by segment at week 48 compared to ISB and BOLS. For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, endoscopic improvements at week 48 will be compared to week 8 of the induction study.
- To evaluate the proportion of patients with glucocorticoid-free clinical remission at week 48.
- To evaluate the effect of ABX464 50 mg QD on stool and rectal bleeding frequency at every study visit compared to BOLS.
- To evaluate the effect of ABX464 50 mg QD on fecal calprotectin and CRP levels at week 24 and week 48 visits compared to BOLS.
- To evaluate the effect of ABX464 50 mg QD on clinical response at week 48 compared to ISB and BOLS. For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, endoscopic measurements at week 48 will be compared to week 8 of the induction study.
- To evaluate the effect of ABX464 50 mg QD on miR-124 expression in colon tissue (RNA later) at week 48 and in total blood at week 24 and week 48.
- To evaluate the effect of ABX464 50 mg QD on patients' quality of Life (QoL) measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at week 24 and week 48 compared to BOLS.
- To evaluate the effect of ABX464 50 mg QD on the rectal/sigmoidal infiltrates using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at week 48 compared to ISB and BOLS. For patients with endoscopic improvements at week 8 of the induction study (ABX464-103) and with no endoscopic data at week 16, endoscopic measurements at week 48 will be compared to week 8 of the induction study.
- To evaluate the long-term safety profile of ABX464 50 mg QD.

Week 96 secondary objectives are:

- To evaluate the effect of ABX464 50 mg QD on partial Modified Mayo Score (pMMS) at every study visit compared to ISB and on Modified Mayo Score at week 96.
- To evaluate the effect of ABX464 50 mg QD on stool and rectal bleeding frequency at every study visit compared to BOLS.
- To evaluate the effect of ABX464 50 mg QD on fecal calprotectin and CRP levels at week 60, 72, 84 and week 96 visits compared to BOLS.
- To evaluate the effect of ABX464 50 mg QD on miR-124 expression in colon tissue (RNA later) and in total blood at week 96.
- To evaluate the long-term safety profile of ABX464 50 mg QD.

Echocardiography objective is:

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

2.3. Primary Endpoint

The primary endpoint is the proportion of patients with clinical remission at week 48 compared to induction study baseline (ABX464-103). Clinical remission, based on the Mayo Scoring system, is defined as stool

frequency sub score = 0 or 1 and rectal Bleeding sub score = 0 and endoscopy sub score = 0 or 1 (modified to exclude friability).

2.4. Secondary Endpoints

The week 24 and 48 secondary endpoints are:

- Reduction relative to baseline in Modified Mayo Score at week 48 and in partial Modified Mayo Score at every study visit among all patients.
- Proportion of patients with either endoscopic improvement or/and endoscopic remission by segment at week 48 among all patients

  Endoscopic improvement is defined as a Mayo endoscopic sub score of ≤1 (excluding friability).

  Endoscopic remission is defined as a Mayo endoscopic sub score of 0.
- Proportion of patients with sustained endoscopic improvement or/and sustained endoscopic remission at week 48.

  Sustained endoscopic improvement is defined as the number of patients with endoscopic improvement at week 48 among patients who had endoscopic improvement during the Induction study (at week 8 or week 16).

  Sustained endoscopic remission is defined as the number of patients with endoscopic remission at week 48 among patients who had endoscopic remission during the Induction study (at week 8 or week 16).
- Proportion of patients with glucocorticoid-free clinical remission at week 48.

  Glucocorticoid-free clinical remission is defined as clinical remission in addition to not requiring any treatment with glucocorticoids for at least 8 weeks prior to week 48.
- Reduction relative to baseline in stool and rectal bleeding frequency at every study visit.
- Reduction relative to baseline in fecal calprotectin and CRP levels at week 24 and 48.
- Proportion of patients with clinical response at week 48.

  Clinical response is defined as: a reduction in Modified Mayo Score ≥ 2 points and ≥ 30 % from baseline with an accompanying decrease in rectal bleeding sub-score ≥ 1 point or absolute rectal bleeding sub-score ≤ 1 point.
- Change relative to baseline in miRNA-124 expression in rectal/sigmoidal biopsies at week 48 and in total blood at week 24 and week 48.
- Scores and changes from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) domains at week 24 and 48.
- Reduction relative to ISB of infiltrate/histopathology (rectal/sigmoidal biopsies) using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at week 48.

The week 96 secondary endpoints are:

- Reduction relative to baseline in Modified Mayo Score at week 96 and in partial Modified Mayo Score at every study visit (week 48 to 96) among all patients.
- Proportion of patients with either endoscopic improvement or/and endoscopic remission by segment at week 96.
- Proportion of patients with sustained endoscopic improvement or/and sustained endoscopic remission at week 96.
- Reduction relative to baseline in stool and rectal bleeding frequency at every study visit (week 48 to 96).
- Reduction relative to baseline in fecal calprotectin and CRP levels at week 60, 72, 84 and 96.
- Proportion of patients with clinical response at week 96.
- Change relative to baseline in miRNA-124 expression in rectal/sigmoidal biopsies and in total blood at week 96.

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 from-previous echocardiogram in Global Longitudinal Strain (GLS).

- Number of subjects with a relative percentage reduction in GLS by > 15% from the previous echocardiogram.
- 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 echocardiogram of other echocardiographic parameters as described in a standard protocol, including 2-dimensional volumes, RV size and systolic function and valve function.

Safety endpoints are:

- Number and rate of all adverse events, causally related adverse events, all SAE and causally related SAEs classified by severity.
- Incidence of treatment-emergent serious adverse event, hospitalizations, total inpatient days.
- Incidence of adverse events leading to investigational product discontinuation.
- Number of clinically significant laboratory abnormalities.

3. INVESTIGATIONAL PLAN

3.1. Study Design

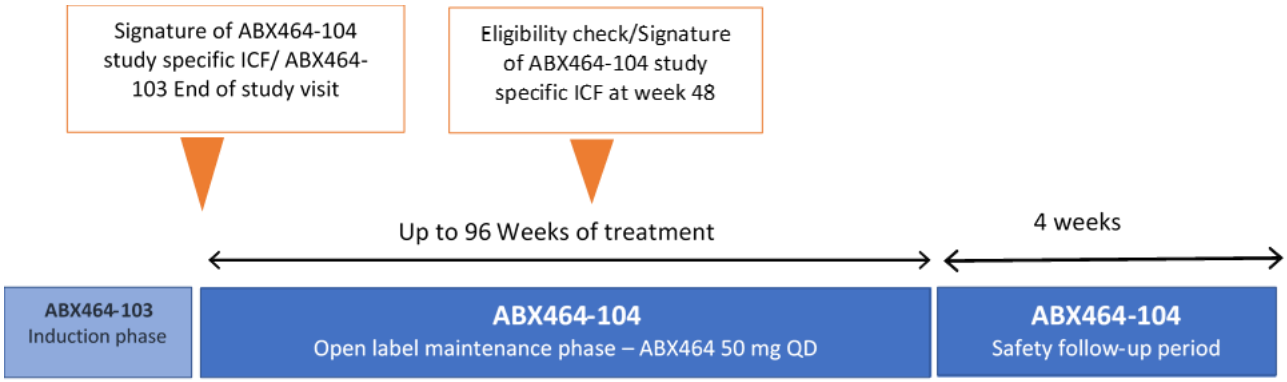
3.1.1. Design and Methodology

This study is an open-label study aiming at evaluating the long-term safety and the efficacy profile of ABX464 given once a day (QD) at 50 mg in patients with moderate to severe ulcerative colitis (UC) who have been previously enrolled in the ABX464-103 clinical study (induction study) and who are willing to receive their treatment with ABX464 as long-term (maintenance) therapy of remission.

All patients who have completed the 16-week (± 4 days) induction treatment period (ABX464-103) will be eligible for this maintenance study regardless of their clinical response and will receive 1 capsule of ABX464 50mg once daily during up to 96 weeks providing the patient has a clinical response at week 48.

The study design is presented below:

Patients will be treated for a maximum of 96 weeks in this maintenance study. After the treatment period, patients will be followed for 4 additional weeks for safety purposes. Alternatively, eligible patients willing to continue study treatment will be offered to take part in a long term follow up safety study (ABX464-108) at the end of treatment (ie Week 96). ABX464-108 study is a separate clinical study requiring health authorities and ethics committees' approvals.



From Day 1 onwards, patients will be seen at the investigational site every 4 weeks up to week 48 and then quarterly until weeks 96. Flexible sigmoidoscopy with rectal and/or sigmoidal biopsies will be performed, for all patients at week 48 and at week 96. Additional flexible sigmoidoscopies may be performed during the open label phase based on medical judgement.

During the open label maintenance phase, in the event of clinical progression of the disease, defined as at least a 2-point increase from the screening partial Modified Mayo Score (pMMS) with a pMMS ≥ 4 confirmed by an endoscopy sub score of 2 points or higher, the patient will exit the study.

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 patients, ensure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial. Besides, the DSMB may recommend the early termination of the trial at any time if an unacceptable toxicity occurs. The DSMB will meet every two months. 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.

3.1.3. Duration of study participation

Patients will receive ABX464 50mg QD for up to 96 Weeks. After the last study drug dose, patients will go through a safety follow-up of 4 weeks. Therefore, the study participation duration will be up to 100 weeks. For subjects who did not meet eligibility at Week 48, the study participation duration will be up to 52 weeks.

4. STUDY POPULATION

4.1. Number of Patients/Centers

Patients will be enrolled in 69 sites located in Europe, US and Canada.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

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

- Patients must have completed the 16-week (± 4 days) induction treatment period (ABX464-103).
- Patients are able and willing to comply with study visits and procedures as per protocol.
- Patients should understand, sign and date the written voluntary informed consent form prior to any protocol-specific procedures are performed.
- Patients should be affiliated to a social security regimen (for French sites only).
- Females and males receiving the study treatment (potentially in combination with immunosuppressant) and their partners must agree to use a highly effective contraceptive method during the study and for 6 months (180 days) after end of study or early termination. Contraception should be in place at least 2 weeks prior to screening. Women must be surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) or in the postmenopausal state (no menses for 12 months without an alternative medical cause) or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (WOCBP) will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception aiming at inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the patient. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle. Female and male patients must not be planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male patients should use condom during the trial and for 6 months (180 days) post completion of their participation in the study. Male patients must not donate sperm as long as contraception is required.

Criteria that should be met by patients at week 48 to be eligible for 48 additional weeks of study treatment.

- Patients should be in clinical response. Clinical response is defined as: a reduction in Modified Mayo Score ≥ 2 points and ≥ 30 % from baseline (induction) with an accompanying decrease in rectal bleeding sub-score ≥ 1 point or absolute rectal bleeding sub-score ≤ 1 point.
- Patients able and willing to continue the study treatment and who are compliant with study visits and procedures and who signed the update of the written voluntary informed consent.

4.2.2. Exclusion Criteria

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

- Patients who permanently discontinued study the treatment in induction study (ABX464-103) because of an adverse event (AE) regardless of relatedness to investigational product.
- Patients who have developed any major illness/condition or evidence of an unstable clinical condition (except UC) that, in the investigator's judgment, will substantially increase the risk to the participant if he or she participates in the study.
- Patients with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
- Patients who are participating in or plan to participate in other investigational studies (other than induction study) during the study.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1. Study Flow Chart

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

	Treatment period							EOS
	Baseline (D113 study ABX464-103)	Week 4 to 20 (every 4 weeks)	Week 24	Week 28 to 44 (every 4 weeks)	Week 48	Week 60 to 84 (every 12 weeks)	Week 96	Week 52 or 100
Time Window		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days
Obtained Inform Consent	X				X#			
Check of IN/EX Criteria	X				X#			
Demographics	X*							
Physical Examination	X*	X	X	X	X	X	X	X
Body Weight (kg)	X*	X	X	X	X	X	X	X
Medical History	X*							
Vital signs	X*	X	X	X	X	X	X	X
ECG (12 lead)	X*				X			X
Concomitant medication	X*	X	X	X	X	X	X	X
Blood Pregnancy test (WOCBP)	X*	X	X	X	X	X	X	X
Hematology + Biochemistry (including NT-proBNP blood levels) ł	X*	X	X	X	X	X	X	X
Modified Mayo Score (partial MMS/MMS)	X*	X	X	X	X	X	X	X
Diary data collection	X*	X	X	X	X	X	X	X
Treatment compliance verification		X	X	X	X	X	X	
Fecal calprotectin	X*		X		X	X	X	X
Serum collection for cytokine assessment	X*		X		X			X
Sigmoidoscopy‡					X		X	
Cardiac ischemic disease/congestive heart failure) medical/treatment history review		X	X	X	X	X	X	
Echocardiography			X		X	Xł	X	
IBDQ	X*		X		X			
ABX464 50mg dispensation	X	X	X	X	X"	X		
Samples for miRNA (Biopsy RNA Later)	X‡				X		X	
Samples for miRNA (Blood PAXgene tube)	X		X		X	X	X	
Adverse Events recording	X	X	X	X	X	X	X	X
Dermatologist Consultation in case of skin effect	*(X)*							

Assessment with an * are not repeated but used from the D113 visit and just re-entered in the CRF
Specific consent and IN/EX for the second year of treatment
‡: Sigmoidoscopy at Week 48 and Week 96 should be performed within a week prior to the visit, to allow the central results to be available at the visit for the assessment of the subject eligibility. Local read results could be used at W96 to assess eligibility of subject to enter ABX464-108 study if central read results are not available.
"If patient is eligible for the 2nd treatment year
ł Only at week 72
ł NT-proBNP blood levels only at Week 24, 48, 72, 96 and at the End of Study Visit
‡Biopsy sample for miRNA is only taken if the conditional sigmoidoscopy at D113 of the ABX464-103 induction study is performed
(X) optional

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. Baseline Visit (i.e. Day 113 of the Induction study ABX464-103)

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

During the baseline visit, the following assessments will be performed (*NB: if some are already performed as per Day 113 of the induction study ABX464-103, results will be captured, but tests must not be repeated*):

- Signed informed consent form
- Inclusion/exclusion criteria will be verified

- Demographic data: date of birth and gender
- IBD Questionnaire (as the first visit procedure)
- Partial Modified Mayo Score
- Hand over paper diary and instruct the patient how to use it
- Medical history
- Record all concomitant medications
- Record previous UC medication without time limitation (Except for conventional treatments such as corticosteroids, oral 5-aminosalicylic acid and immunosuppressants which are to be recorded within a year prior to baseline)
- Physical examination including body weight and vital signs measurements
- 12 leads ECG
- Hematology and Biochemistry including pregnancy test for all women of childbearing potential
- Serum tube collection (Cytokines)
- Tissue samples for miRNA (Biopsy RNA Later) if conditional sigmoidoscopy performed on Day 113 of the induction study ABX464-103 (sampling must not be repeated)
- Blood sample for miR-124 dosage (PAXgene® tube) if performed on Day 113 of the induction study ABX464-103, sampling must not be repeated)
- Fecal calprotectin
- Dispense study treatment to patient and instruct to take the first capsule of the ABX464-104 medication the next day of the visit due to the PK samplings in the frame of the ABX464-103 study (no PK analysis is performed in the frame of the study ABX464-104)
- Adverse Event reporting. *In case of a skin effect, please refer to a dermatologist*
- *Optional: sigmoidoscopy with biopsy (if performed during the D113 visit of ABX464-103, data will be recorded for the ABX464-104 study protocol)*
- Schedule next patient visit (i.e. week 4).

5.2.2. Monthly and Quarterly Visits (W4, week X+4; W48, week X+12 and W96)

- 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
- Physical examination including body weight and vital signs measurements
- Hematology and Biochemistry (Including NT-proBNP levels at week 24, week 48, week 72and week 96)
- Blood pregnancy test for all women of childbearing potential
- Record all concomitant medication change
- Check treatment compliance and review the patient diary
- Partial Modified Mayo Score
- Fecal calprotectin (at week 24 and week 48 and then quarterly)
- Blood sample for miR-124 dosage (PAXgene® tube) (at week 24 and week 48 and then quarterly)
- Adverse Events reporting. *In case of a skin effect, please refer to a dermatologist*
- Dispense the study treatment needed to cover the period between consecutive visits (except at Week 48 if patient is not eligible for a second year of treatment; no dispensation of IP at Week 96)
- Schedule next patient visits (At W96 schedule EOS visit if subjects not rolling over to the long term follow up safety study (ABX464-108).

To be performed additionally at week 24 and week 48:

- IBD Questionnaire (prior to other study procedures)

- Serum collection for cytokine assessment
- Echocardiography.

To be performed additionally at week 48 only:

- ECG (12-lead)
- Sigmoidoscopy with rectal/sigmoidal biopsies for miRNA assessment (procedure can also be done at interim study visits only if medically justified); Sigmoidoscopy should be performed within a week prior to the visit, to allow the central results to be available at the visit for the assessment of the subject eligibility to the second year of treatment
- Check of patient's eligibility for a second year of treatment
- Second year patient consent signature.

To be performed additionally at week 72:

- Echocardiography.

To be performed additionally at week 96:

- Sigmoidoscopy with rectal/sigmoidal biopsies; Sigmoidoscopy should be performed within a week prior to the visit, to allow the central results to be available at the visit for the assessment of the subject eligibility to the long term follow up safety study (ABX464-108). Local read results could be used at W96 to assess eligibility of subject to enter ABX464-108 study, if central read results are not available.
- Echocardiography
- Enrolment of eligible subjects willing to take part to the long term follow up safety study (ABX464-108).

5.2.3. End of Study Visit (Week 52 or Week 100 ± 2 days)

This EoS visit applies to all premature discontinued patients, to all patients who completed the W48 treatment phase and who are found non-eligible for the second year of treatment and for patients not taking part to the long term follow up safety study (ABX464-108). Patients will perform an End of Study Visit (EoS) 4 weeks after last study drug intake (i.e Week 52 ± 2 days if the patient did not meet eligibility criteria at week 48; Week 100 ± 2 days if the patient completed the study and is not taking part to the long term follow up safety study (ABX464-108).

Following examinations/procedures should be performed:

- Physical examination including body weight and vital signs measurements
- ECG (12-lead)
- Hematology and Biochemistry (Including NT-proBNP levels)
- Blood pregnancy test for all women of childbearing potential
- Record all concomitant medication change
- Check treatment compliance and review the patient diary
- Partial Modified Mayo Score
- Fecal calprotectin
- Serum collection for cytokine assessment
- Adverse Events reporting. *In case of a skin effect, please refer to a dermatologist*

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. Echocardiography will be performed at the earliest opportunity (Week 24 or Week 48 or Week 72) and will be repeated every six months. Two-dimensional echocardiography measurements will be assessed during the study. Echocardiography will be performed locally, and the images will be transmitted to a central reading vendor (Clario) for independent read and evaluation. Sites will receive appropriate training as well as an Echocardiography Manual that includes detailed instructions regarding image acquisition, test echo submission/approval and image upload procedures.

Central assessments will adhere to the recommendations of the American Society of Echocardiography.

In addition, local reads must be performed by site in the case central evaluation is not possible and results will be recorded in EDC.

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 (RV) size and systolic function assessment

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.

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 patient should rest supine for at least 10 minutes prior to measurements. The measurements can be performed either in sitting or supine position of the patient. The right or left arm may be used. However, the position and the arm used for measurement should be kept constant throughout the trial for an individual patient.

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

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 patients of childbearing potential, a blood pregnancy test (beta human chorionic gonadotropin [HCG]) will be performed at every visit. In case of positive pregnancy testing, detailed procedures can be found in section 8.7.2.

Urine pregnancy tests will be supplied to female patients of childbearing potential from week 48 onwards to test for potential pregnancy every month. She will be instructed by the site how to use them and to contact immediately the site in case of positive result.

5.3.5. ECG

Electrocardiograms will be performed at baseline, week 48 and 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) will be measured at a resting position. Prior to the recording the patient 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. If thermal paper is used, a copy of the original ECG must also be kept. All abnormal findings must be documented in the CRF. Any clinically relevant findings compared to ECG done at Day 0 must be documented as adverse events.

5.3.6. IBD Questionnaire (IBDQ)

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a widely used questionnaire for patients' quality of life assessment in patients with inflammatory bowel diseases (IBDs). This questionnaire has been adapted and validated into several languages. IBDQ will be filled in by the patients at baseline, week 24 and week 48 prior to any study procedures.

5.3.7. Modified Mayo Score - Stool and Rectal Bleeding Frequency

The Stool and Rectal Bleeding frequency assessment will be based on the Mayo scoring system which is the most commonly used index in clinical trials.

While Total Mayo score consists of 4 items: stool frequency, rectal bleeding, flexible sigmoidoscopic examination, and a physician global assessment (Appendix #3), in this study and according to regulatory guidance, the physician global assessment has been removed to define the Modified Mayo Score (MMS).

Partial Modified Mayo Score (pMMS) consists of only 2 items (stool frequency, rectal bleeding). Stool frequency and rectal bleeding frequency will be recorded from the patient diary at each patient visit by the Investigator.

Instruction for Mayo Score Calculation (MMS/pMMS) is provided in appendices (Appendix #6).

Attention: Investigators should train his/her patient how to record stool frequency and rectal bleedings in the diary. Instruction booklet, detailing the FDA requirements for Patient Reported Outcomes, will be provided to patients and investigators.

5.3.8. Sigmoidoscopy with rectal/sigmoidal biopsies

Sigmoidoscopies procedures (or colonoscopies if applicable) will be performed by the site endoscopist. Bowel preparation is mandatory. Patients will be instructed to follow the site standard of care.

Procedures 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 and visit sequence of the recordings.

The central reader's score at baseline (ABX464-103 / W8 or W16), week 48 and week 96 will be entered directly into the eCRF. All procedure videos collected for outcome evaluation will be scored and results communicated within five (5) business days.

Two rectal biopsies (plus optionally two sigmoidal biopsies, if the inflammation of the sigmoid is observed) will be performed at week 48 and 96. The biopsies (1+1 back-up for each test) will be sent to central laboratories

for assessment according to Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales (please refer to the lab manual) and for miRNA-124 determination (RNA later).

RHI score ranges from 0 (no disease activity) to 33 (severe disease activity) and is based on the evaluation of four main parameters: chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in the epithelium and erosion/ulceration. Overall, this histological index has been reported to be reproducible, responsive and valid and will be used for confirmation of the mucosal healing. The patient's biopsies will be also read according to the Geboes and Nancy Histology Scoring Scales for completeness purposes.

5.3.9. Hematology, biochemistry and calprotectin evaluation

For hematology and biochemistry central laboratory will be used (i.e. Eurofins). All lab dosages will be done centrally (except with prior approval). Sampling kits and transportation information and devices will be provided by Eurofins.

Regarding the calprotectin measurement, the site might be asked to keep back-up samples at -80°C till the end of the study.

Any hematology and biochemistry safety sample (Total bilirubin, AST/ALT, Alkaline phosphatase, Lipase INR, Prothrombin, Troponin I & T, CPK and NT-proBNP) that does not have a result reported at any visit must be repeated by the central lab (or locally if preferred).

For the containment and countering against the spread of the COVID-19 virus (coronavirus disease 19), safety blood tests (such as but not limited to LFTs, WBC and hemoglobin) may be performed in other facilities. Laboratory reports should be reviewed, dated and signed by the principal investigator and kept in the medical file of the subjects. This waiver should also be extended to additional safety procedures for the subject, including, for example, cardiological and radiological tests and procedures.

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

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

Table 2 displays the clinical laboratory parameters that must be measured.

Table 2: Laboratory Tests

HEMATOLOGY PANEL	BIOCHEMISTRY PANEL		IMMUNOCHEMISTRY	STOOLS
Hemoglobin Hematocrit WBC Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelet count Fibrinogen Prothrombin time	Sodium Potassium Chloride Calcium Phosphate Glucose BUN or urea Creatinine CPK AST ALT Total, HDL and LDL cholesterol	Lipase Alkaline phosphatase gammaGT Total bilirubin Total protein Albumin LDH CRP GLDH NT-proBNP Amylase	Troponin I & T T3, T4, TSH β-hCG	Fecal calprotectin

5.3.10. Cytokines analysis

Cytokines (such as IL-6, TNFα, IL-1b, IL-10, MCP-1 but not limited to) will be assessed by a central laboratory.

All samples will be kept on site (-20°C/-80°C) until sponsor's notification for shipment to the central laboratory. The process for samples preparation, storage and shipment will be fully defined in the laboratory manual.

5.3.11. miRNA modulation

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

The rectal/sigmoidal biopsies will be stored in RNA later, total blood in PAXgene® tubes according to lab manual instructions.

5.4. Summary of blood samples

The table 3 below summarizes the volume of blood to be sampled at each study visit. A total of 316 ml should be needed if the patient does not take part to the second year of study treatment or a total of 418 ml for the whole study duration including the second year.

Table 3: Blood Volume

	Collection tube	**Baseline***	**Week 4 to Week 20 (5 visits)**	**Week 24**	**Week 28 to Week 44 (5 visits)**	**Week 48**	**EOS D52/week 52 or week 100**	**Total Per Panel**
Hematology (Hemoglobin, Hematocrit, Red Cell Count, MCV, MCHC, Platelets, White cell count with diff.)	EDTA tube	2	2	2	2	2	2	**12**
Biochemistry panel incl CRP, GLDH, CPK, Serum Pregnancy test and lipids	Serum gel tube	8,5	8,5	8,5	8,5	8,5	8,5	**51**
Fibrinogen and Prothrombin Time	Na-citrate tube	4,5	4,5	4,5	4,5	4,5	4,5	**27**
NT-proBNP	K2 EDTA tube	2		2		2	2	**8**
Troponin (I&T)	SST tube with gel	3,5	3,5	3,5	3,5	3,5	3,5	**21**
Cytokines (IL-6, TNFa, IL-1b, IL-10)	Serum gel tube	8,5		8,5		8,5	8,5	**34**
PAXgene Tube (miRNA)	PAXgene			5		5	5	**15**
	Total per visit	**29**	**18,5**	**34**	**18,5**	**34**	**34**	

*To be done if testing was not performed in the ABX464-103 study. Otherwise, results are to be collected only.

	Collection tube	**Week 60 to Week 96 (4 visits)**	**Total Per Panel**
Hematology (Hemoglobin, Hematocrit, Red Cell Count, MCV, MCHC, Platelets, White cell count with diff.)	EDTA tube	2	**8**
Biochemistry panel incl CRP, CPK, GLDH, Serum Pregnancy tests, amylase and lipids	Serum gel tube	8,5	**34**
NT-proBNP	K2 EDTA tube	2	**8**
Fibrinogen and Prothrombin Time	Na-citrate tube	4,5	**18**
Troponin (I&T)	SST tube with gel	3,5	**14**
miRNA	PAXgene Tube	5	**20**
	Total per visit	**25.5**	**102**

6. INVESTIGATIONAL PRODUCT(S)

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

6.1. Description of investigational treatment

The study treatment that will be administrated to patients enrolled in this phase 2b study consists of capsules containing ABX464 50mg given orally once daily for a maximum of 96 weeks.

6.2. Description of investigational Product ABX 464

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

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

It is supplied in high-density polyethylene (HDPE) bottles closed with child-resistant polypropylene screw caps.

ABX464 manufacturing and packaging will be performed at the following site:

DELPHARM Lille SAS

Parc d'activité Roubaix Est

22, rue de Toufflers

CS 50070

59 452 Lys-Lez-Lannoy France

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

Creapharm S.A.S.

Z.A. Air Space

Avenue de Magudas CS 2007

33187 Le Haillan

France

6.3. Administration and Dosing

6.3.1. Administration of the investigational product

Patients will be treated with a daily dose of 50mg of ABX464. Patients will receive 1 capsule every day. starting the day after the baseline visit. All patients will be orally dosed in a fed condition (regular meal) with a glass of water. A patient diary, in which the patient should report the daily number of capsules taken and the intake time will be given to the patient at baseline.

6.3.2. Guidelines for treatment postponement and dose modifications

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

6.4. Method of Assigning Patient Numbers

All patients will be assigned a unique and incremental Patient Identification (ID) number (same number as the one used in the ABX464-103 study). Patient IDs will be unique (i.e. reallocation of the ID will not be permitted). The format will be a seven-digit number as follows: site number (4 digits) – Patient number (3 digits). The latter 3-digit Patient number will be assigned according to the patient's order of inclusion in the center.

Eligible patients (i.e. those who fulfil all inclusion/exclusion criteria) will all receive active treatment. In all cases, patients should return his/her used and unused HPDE bottles at each study visit for a compliance check. Patient's compliance to treatment (including capsule count) will be recorded on the eCRF. Insufficient treatment compliance (compliance < 80% and non-respect of administration scheme) will be reported as deviations.

6.5. Packaging

The IMP consists in hard gelatin, powder-filled capsules (size 01) containing 50 mg of ABX464 supplied in HDPE (high-density polyethylene) bottles closed with child-resistant polypropylene screw caps (30 capsules per bottle).

6.6. Storage

ABX464 capsules will be shipped to the investigational site at a temperature not above 25°C (77°F).

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

The IMP must not be used beyond the expiration date. Drug supplies are to be stored in a secure, limited-access location under the storage conditions as specified in the IMP manual.

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 or 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

Allowed Concomitant Medications are:

- Oral 5-aminosalicylic acid at stable dose [9];
- Immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate at stable dose;
- Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) at stable dose;
- For patients on oral corticosteroids at baseline, prednisone or prednisone equivalent ≤20 mg/day; beclomethasone diproprionate (≤5mg/day) or budesonide MMX (≤9 mg/day).

Tapering period:

For patients on oral corticosteroids at baseline, a tapering of steroids should be performed from baseline onwards. The rate of prednisone or prednisone equivalent tapering should not exceed 5 mg/week till complete discontinuation. The tapering can be stopped at any time based on medical judgment. No further oral corticosteroids dose escalation is 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 patient and the eCRF.

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

6.8.2. Prohibited concurrent medications

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

- Tumor necrosis factor [TNF] inhibitors, vedolizumab or others biologic therapies.
- JAK inhibitors.
- Topical corticosteroids and topical 5-aminosalicylic acid preparations.
- Cyclosporine and tacrolimus.
- Vaccination with live components during the study and up to 8 Weeks after the last dosing (COVID 19 vaccines are allowed).
- Drugs that inhibit or induce CYP1A2 (Appendix #1).
- Drugs that inhibit UDP-glucuronosyltransferase (UGT) IA9 activity and inhibitors or substrates of organic anion transporter (OAT) P1B1/P1B3 transporters (Appendix #1).
- Use of any investigational or non-registered product.

7. STUDY COMPLETION AND WITHDRAWAL

7.1. Patient Completion

Treatment with ABX464 shall continue until Week 48 (if the patient did not meet eligibility at week 48 to continue treatment until Week 96) or until week 96, except if a patient fulfils a premature discontinuation criterion (defined below).

7.2. Premature trial discontinuation

Subjects who are not found eligible for the second year of treatment are not considered as prematurely discontinued as they have completed the first-year treatment. A patient can be withdrawn at any time from the study for the following reasons:

- Investigator's decision: 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
- 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 the abnormality stabilizes after this 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%).
- A 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 study subjects;
- New onset of acute pancreatitis;
- Malignancies (including non-melanoma skin cancers);
- Medically significant abnormal laboratory results, including new onset anemia (defined as a hemoglobin decrease >2 g/dL from baseline or hemoglobin <8 g/dL) - note: transient abnormal values, and/or abnormal values related to an existing condition that doesn't constitute a worsening will not be a criteria for discontinuation.
- 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.
- Worsening of the UC defined, from the baseline visit of the maintenance phase onwards, as a 2-point increase in the partial MMS, with pMMS ≥ 4 on 2 separate occasions 7 day-apart and confirmed by an endoscopy sub-score of 2 points or higher. In such a case the patient will be withdrawn from the study.
- 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.

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

7.3. Study Discontinuation

All patients, regardless of the completion or premature discontinuation, should perform the End of Study Visit according to the study flow-chart.

7.4. Baseline Failures

A patient is considered to be a baseline failure if the patient signs the informed consent but withdraws before first dosing in the maintenance phase. Reasons for exclusion will be recorded for potential patients who do not enter the study.

7.5. End of Trial

The ABX464-104 is the maintenance phase of the ABX464-103 protocol (induction study). ABX464-104 End of Trial will occur once the last patient from the induction study completes the last study visit.

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 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.

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

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

8.2. Definition of an AESI

The following events will be considered AESIs and must be reported using the AESI forms.

Skin Lesions (regardless of its severity)

The AESI “skin lesion” should be broadly captured by the site physician. Subjects are informed via the ICF that oral administration of ABX464-N-Glu was phototoxic in a nonclinical model at clinically relevant exposure levels. To mitigate this risk, subjects must comply with usual public recommendations for sun protection, such as: use shade wisely, wear protective clothing (hat, sunglasses), use sunscreen (with a sun protective factor [SPF] of 15 or higher), and limit time spent in mid-day sun or strong sunlight. Subjects experiencing skin lesion(s) will be instructed to contact the site study coordinator or investigator and to take a picture of the skin lesion for medical assessment. The site investigator will complete a specific skin lesion AESI reporting form (Appendix # 4). Additionally, the skin lesion AESI form may be supplemented by pictures of the affected skin region(s) taken by the subject, at their discretion. The pseudonymized skin lesion AESI form will be reviewed by a central dermatologist, to investigate a potential for photosensitivity. A pseudonymized medical report will be provided by the central dermatologist.

Headaches

Headaches are frequently reported by subjects dosed with ABX464. In specific situations (i.e. the headache lasts more than 72 hours AND is not resolved by standard painkillers), the AE will be closely monitored by means of an individually adapted questionnaire (Appendix #5), and sent to VCLS together with the AESI form.

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 haemoglobin and haematocrit levels.

Anemia defined as a Hemoglobin drop > 2 g/dL from baseline or Hemoglobin < 8g/dL will be reported as AESI.

Hepatic enzymes

ABX464 showed hepatoxicity findings in pre-clinical 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 available data, a DILIsym evaluation of ABX464 and ABX464-N-Glu has indicated no predictors of toxicity. 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 testes (LFTs). No Hy's Law cases have been observed in ABX464 subjects. Sporadic cases of isolated alkaline phosphatase increase have been reported in subjects dosed with ABX464.

An increase ≥ 3.0 × ULN in liver transaminases (AST and/or ALT) or an increase ≥ 2.0 × ULN in total bilirubin without initial findings of cholestasis (elevated alkaline phosphatase) will be reported as an 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 subjects as well as in subjects 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 [12].

The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) 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. 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.

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, 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 all patients:

- Monitoring of AST, Troponin, and creatine phosphokinase blood levels at each study visit, including baseline visit and End of Study Visit.
- Monitoring of N-terminal pro b-type natriuretic peptide blood levels at baseline, and week 8. A relative change of more than 20% from baseline values will be reported as an AESI.

Two-dimensional echocardiography will be performed in subset of subjects.

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 TEAEs will be also categorized as cardiac AESI: 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 an Adverse Drug Reactions (ADR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

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

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

8.5. 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 patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires hospitalization or prolongation of existing hospitalization

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

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

d) Results in persistent or significant disability/incapacity,

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

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

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

8.6. 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).

8.7. Events or Outcomes Qualifying as AEs or SAEs

8.7.1. 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 8.5 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 patient's condition, then they may be reported as AEs or SAEs.

8.7.2. Pregnancy report

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

The investigator will collect pregnancy information on any woman patient or partner of a male patient, who becomes pregnant and their partner while participating in this study. The partner of a male patient will sign an Informed Consent Form before the pregnancy data can be collected. The investigator will record pregnancy information on a specific pregnancy notification form and submit it to ABIVAX or its designee within 24 hours after knowledge of a patient's or partner's pregnancy. The patient or partner will also be followed to determine the outcome of the pregnancy, be it full-term or prematurely terminated. Information on the status of the mother and child will be forwarded to ABIVAX or its designee. Follow-up will 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 8.8, 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.

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

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

Moreover, any occurrence of pregnancy within 6 months post stopping dosing must be reported by using the specific pregnancy reporting form and sent to VOISIN CONSULTING LIFE SCIENCES (VCLS).

Importantly, SAEs and AESI will have to be reported, either by email to VCLS immediately after becoming aware of the SAE/AESI, within 24 hours of awareness at the very latest.

VOISIN CONSULTING LIFE SCIENCES (VCLS)

E-mail: abivaxsafety@voisinconsulting.com

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

8.9. Recording AEs and SAEs

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

Any ongoing AE from the ABX464-103 study is reported as medical history, any worsening of condition that started as an AE in the 103 study is to be reported as a new AE.

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

The following points must be recorded for each event:

- A description of the event in medical terms, not as reported by the patient
- Date of onset (start date)
- Date of resolution (stop date)
- The time of onset with respect to administering the investigational product
- The severity of the sign/symptom or clinically significant abnormal laboratory value according to CTC-AE Classification (v5.0)
- 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.
- AE outcome:
  - Recovered without sequelae / resolved without sequelae
  - Recovered with sequelae / resolved with sequelae
  - Recovering/Resolving
  - On-going
  - Fatal (for SAEs only).

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

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

Throughout the study, the reporting of AESIs/SAEs 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 VCLS **immediately after becoming aware of the SAE/AESI, within 24 hours of awareness at the very latest.**

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

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain.

Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

An assessment of causality must 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 must not wait to receive additional information before completing the form and notifying VCLS.

Additional or follow-up information relating to the initial SAE/AESI report, will be requested, if necessary. Again, this information is to be completed and submitted through the SAE/AESI 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 must notify VCLS by telephone within the given timeframe and send a copy of the SAE/AESI report form by email.

8.11. Reporting of SAEs to Regulatory Authorities

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

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

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

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

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

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

9.1. Statistical and Analytical Plans

An interim analysis is planned once all the subjects have completed the Week 48 visit. The final study analysis will be performed following database lock upon the completion of the last patient or upon its early discontinuation whichever occurs first.

9.1.1. Protocol deviations

Protocol deviations will be reviewed and classed as critical, major or minor during the blind-review meeting.

9.1.2. Definition of study analysis sets

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

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

9.1.3. Patients/Patients disposition

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

9.1.4. Demographic and other baseline characteristics

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

9.1.5. Treatment compliance

Subject's compliance to treatment (including capsule count) will be recorded on the eCRF. Number of daily doses will be presented on the FAS population. Insufficient treatment compliance (compliance < 80% and non-respect of administration scheme) will be reported as deviations.

9.1.6. Interim analysis

An interim analysis will be performed when all the subjects reach Week 48 visit. The interim analysis will include safety and efficacy data such as the following data: (a) Reduction relative to baseline in Modified Mayo Score and in partial Modified Mayo Score at every study visit among all patients (b) Clinical response and remission, endoscopy improvement and remission (c) Glucocorticoid-free clinical remission at week 48 (d) Fecal calprotectin results (e) Safety parameters (f) Hematology and biochemistry parameters.

9.2. Efficacy Analysis

Descriptive statistics will be presented for all efficacy variables for each measurement timepoint.

In addition, subgroup descriptive analysis will be performed according to the patient status at the end of the induction study (remitter, responder or non-responder), and the treatment received during the induction phase (ABX464 25 mg, 50 mg or 100 mg, or matching placebo).

9.3. Safety Analyses

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

Analysis of safety will be performed on the safety data set consisting of all patients who received at least one dose of ABX464 in the study. The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the “CTC-AE” (Version 5.0) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values.

Adverse events will be tabulated (counts and percentages). 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. Frequency and percentage of patients and number of occurrences of adverse events will also be presented for serious TEAEs, TEAEs leading to study drug discontinuation, discontinuation from the study or death and TEAEs of special interest.

Clinical laboratory parameters, including echocardiography parameters, and vital signs will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Frequency and percentage of patients with normal, abnormal and abnormal clinically significant ECG results will also be summarized. The number of patients with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables.

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

This study is an open label extension study. Sample size calculation is therefore 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 / IQVIA 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.
- 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.
- 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.

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

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

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

10.1.2. Independent Ethics Committee/Institutional Review Board

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

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

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

10.1.3. Patient Informed Consent

It is the responsibility of the investigator to give each patient full and adequate verbal and written information regarding the aims, methods, anticipated benefits and potential hazards. The patient must be informed that

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

The 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. Patients should be informed about the purpose of the planned computer data processing and the publication of the data (e.g. at scientific meetings). The patient must give consent to the computer processing and to the publishing of anonymous data.

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

10.1.4. Compensation to Patients

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

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

11. STUDY MANAGEMENT

11.1. Remote Data Entry

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

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

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

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

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

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

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

11.2. Data management

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

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

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

11.3. Data coding

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

11.4. Study Monitoring

The study will be conducted in accordance with the related topic of the ICH E6 (R2) GCP guidelines. The appointed monitor will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ABIVAX requirements. Throughout the study, the monitor will arrange visits to the study center at appropriate intervals to assess the progress of the study and review the completed eCRFs. 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 patients are being protected;
- Check that the data are authentic, accurate, and complete and discuss any inconsistencies;
- Ensure that all study materials are correctly stored and dispensed with particular emphasis to the investigational product;
- Verify that the site staff and facilities continue to be adequate for the proper conduct of the study;
- Ensure that the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements;
- Help resolve any problems that may have arisen.

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

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 E6 (R2) section 4.9, any institutional requirements or local laws and regulations, or ABIVAX standards/procedures; otherwise, by default the retention period will be 15 years.

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

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

11.7. Study and Site Closure

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

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

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

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

11.8. 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 patients, as appropriate.

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

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

11.9. Ownership and Confidentiality

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

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

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13. APPENDICES

Appendix 1: CYPIA2 **inhibitors/inducers, OATP1B1/P1B3 inhibitors and** substrates**, UGT1A9 inhibitors**

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

Inhibitors: Artemisinin, Atazanavir, **Ciprofloxacin, Enoxacin**, Ethinyl Estradiol, **Fluvoxamine,** Mexiletine, Tacrine, Thiabendazole, Zileuton Inducers: **Montelukast, Phenytoin, Rifampicin, Ritonavir, Teriflunomide**

OATP1B1/P1B3 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: IBD Questionnaire

IBD Questionnaire (English Version)

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your
because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been lo
Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option fr

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needi
have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engag
because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abd
Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose ar
from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not f
a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure
activities you would have liked to have done during the last 2 weeks? Please ch
option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LE
ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen?
choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's s
been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Pleas
choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing l amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or gettir the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illn These include: worries about getting cancer, worries about never feeling any better, worries about having a relapse. In general, how often during the last 2 weeks have yo worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choc an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleed with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of y bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling o to go to the bathroom even though your bowels were empty? Please choose an opti

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidenta of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of you problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 we Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or fe sick to your stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choos option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from oth Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the p weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASE

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 : SKIN LESION QUESTIONNAIRE (for Investigators)

Subjects should be asked to take picture of any skin lesion

Study/Subject Details		
Study number:		
Subject number:	**Age at Onset of Event:**	**Gender: Male Female**

Additional Medical History, please mention if		
○ **Photosensitivity?**	**Yes**	**No**
○ **Drug(s) allergy?**	**Yes**	**No**
○ **Cutaneous adverse drug reaction?**	**Yes**	**No**
Other Dermatologic Medical History		

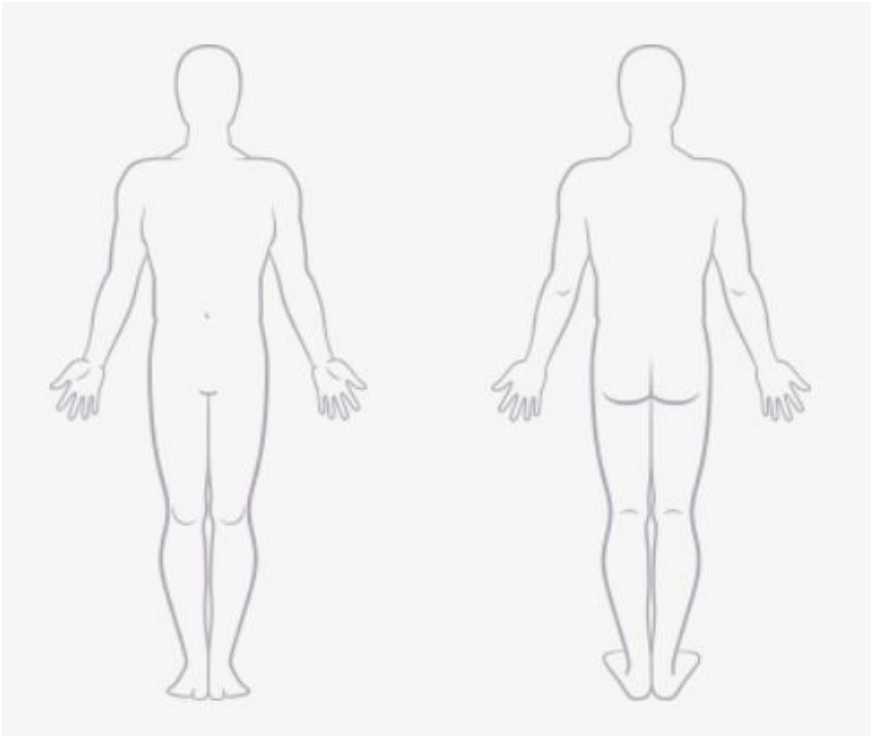
Last intake of ABX464 before the event	**Date:**	**Hour:**

Skin lesion(s):	
○ **Start date** **Hour:**	
○ **End date**	**Ongoing**

Type of skin lesions:			
○ **Rash, macular**	**Yes**	**No**	**Please precise the size and the color of the lesions:**
○ **Rash popular**	**Yes**	**No**	
○ **Rash maculopapular**	**Yes**	**No**	
○ **Rash vesicular**	**Yes**	**No**	
○ **Urticaria**	**Yes**	**No**	
○ **Eczematous**	**Yes**	**No**	
○ **Pustules**	**Yes**	**No**	
○ **Other: Precise**			

Skin lesion associated with sun exposure? **Yes** **No** **If Yes:**
How long after sun exposure did this occur?

Minutes	Later that day	Next day	Within 1 week
Which parts of the body are affected?			
Exposed areas		**Unexposed areas (remember that thin clothes have only a low SPF)**	
Topography of skin lesions:			



Were pictures taken? Yes No
(If answer is Yes, please join pseudonymized pictures)
Consultation with a dermatologist? Yes No
(If answer is Yes, please join the pseudonymized dermatologist consultation report)
Skin biopsy? Yes No
(If answer is Yes, please join the pseudonymized skin biopsy report)

Medications and medical measures (which have been taken) to treat the skin lesions

Study drug discontinued or interrupted due to this event? Yes No
If Yes, dates of study drug discontinuation/interruption:

Reporter Details

Title:	Name:	Role:
		Date:

Pseudonymized picture of the skin lesion
(Date and hour should be outlined on each picture)

Picture

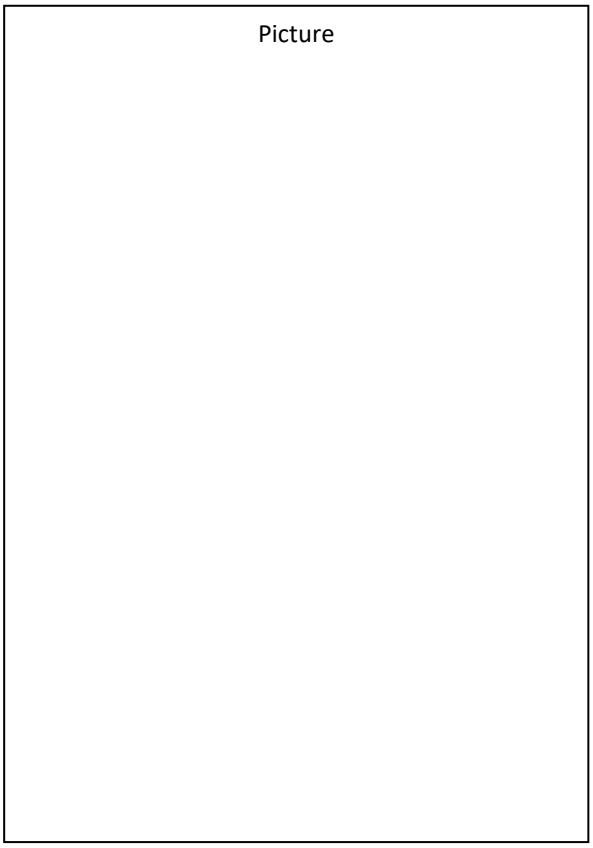
Picture 1

Picture Date : / / time: :

Skin Lesion Start Date : / / time: :

Evolution of the skin lesion

Picture



Picture 2

Picture Date : / / time: :

Skin Lesion Start Date : / / time: :

Appendix 5: Headache Questionnaire

Headache Questionnaire

Questionnaire to be completed if the Headaches meet the following criteria: Headache lasting longer than 72 hours and not resolved by standard painkillers.

Subject ID: _____ **Year Of Birth:** _____ **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?

◯ 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

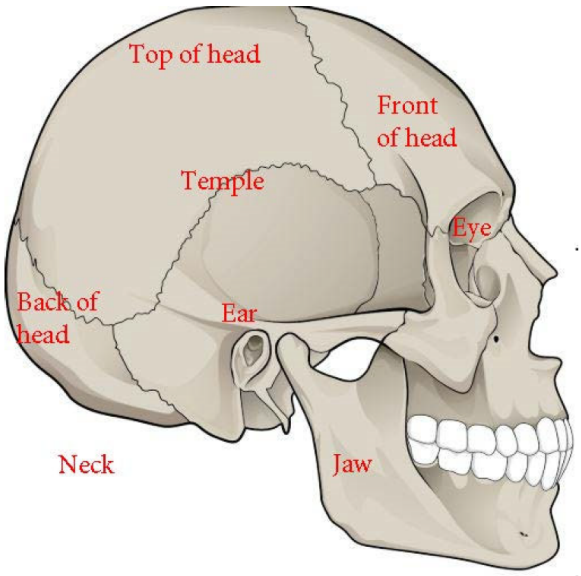
**If YES to above, please focus the following questions on your worst disability headache type*

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 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

11. 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?

12.

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: _____	

Appendix 6 : MAYO Score Calculation

Components of the MAYO score:

Partial modified Mayo Score (pMMS) calculation includes the "Stool frequency" and "Rectal bleeding" components but does not include the "Mucosal appearance at endoscopy" component.

Modified Mayo Score (MMS) calculation includes the Stool Frequency", Rectal bleeding" and the "Mucosal appearance at endoscopy" components. MMS is calculated at the visit where the sigmoidoscopy is performed.

Mayo score (modified, partial modified) is to be calculated at indicated study visits.

Stool Frequency and Rectal Bleed sub-score: Instructions and Calculation

I. NORMAL number of stools for the subject.

At the screening visit (during the 103 study), the subject filled in the average number of stools per day while he/she was in remission as the baseline number of stools. If the subject has never been in remission, then he/she will enter the average number of stools per day before he/she was diagnosed with Ulcerative Colitis. This number will be considered as the "normal" number of stools for the subject and this number is taken from the ABX464-103 study.

II. Stool Frequency and Rectal Bleeding scores calculation rules:

- The calculation of Stool frequency and Rectal bleeding sub-scores at a visit are based on stool number and rectal bleeding of the most 3 recent last values within last 7 days prior to the visit.
- At visits where there is endoscopy performed, the most recent consecutive 3 days preceding the sigmoidoscopy and excluding the day of bowel preparation should be considered for the calculation of the average number of stool and the rectal bleeding.
- Only days when the number of stool and the rectal bleeding are available will be considered for the calculation.
- If some of the data are missing from the most recent consecutive 3 days preceding the visit, then data from the next closest days within the week before the visit will be used for the calculation.
- For the calculation of Stool frequency and Rectal bleed sub score usual rounding rules apply.

III. Stool frequency and rectal bleeding scores calculation:

- Sub scores of Stool Frequency are calculated based on the Number of stools/days ***more than*** **the normal number.** The average of the most recent 3 days within the week before the visit will be used for the calculation of the sub score of Stool Frequency.
- Sub scores of Rectal Bleeding are based on Categories of Rectal Bleeding. The worst category of the most recent 3 days within the week before the visit will be used for the calculation of the sub score of Rectal Bleeding.

IV. RB and SF Sub scores calculation: Example

N= 1

Day	Day - 7	Day - 6	Day - 5	Day - 4	Day - 3	Day - 2	Day - 1	Visit Day
Date (**DD/MM**)								
Nb of stool for each day					1	3	2	
No blood seen								
Visible blood with stool less than half the time					X		X	
Obvious blood (more than just streaks) or streaks of blood with stool most of the time						X		
Blood alone passed								

For the calculation of Stool frequency sub score:

In this example above:

- N (Normal stool frequency) = 1
- Stool frequency = Mean (Day -1; Day -2; Day -3) = Mean (2; 3; 1) = (2+3+1)/3 = 6/3 = 2
  - Stool Frequency = [(mean of Stool Frequency) – (the normal number)] = [(2)-(1)] = 1
  - Stool Frequency Subscore = 1 on the Mayo scale which corresponds to "1-2 stools/day more than normal".
- **Hence, the sub score for Stool Frequency = 1**

For the calculation of Rectal bleeding sub score:

- The worst score of the 3 days (Day -1, Day -2 and Day -3) is used. In this case, "obvious blood (more than just streaks), or streaks of blood with stool more of the time" on Day -2.
- **The Rectal bleeding sub score = Worst bleeding category = 2 =** "obvious blood (more than just streaks), or streaks of blood with stool more of the time""
  - Hence the Rectal bleeding sub score = 2