CLINICAL STUDY PROTOCOL
ABX464-103

Sponsor:	ABIVAX 5, rue de la Baume 75008 Paris FRANCE
Investigational medicinal product:	Not Available
Product code:	ABX464
Study Title:	A randomized, double blind, placebo controlled, parallel group, multiple dose, induction study to evaluate the safety, tolerability and optimal dose of ABX464 compared with placebo in patients with moderate to severe ulcerative colitis who have inadequate response, loss of response, or intolerance with at least one of the following agents: immunosuppressant treatment (i.e. azathioprine, 6-mercaptopurine, methotrexate), tumor necrosis factor alpha [TNF-α] inhibitors, vedolizumab, JAK inhibitors and/or corticosteroid treatment.
EudraCT number:	2018-003558-26
IND Number:	141.396
Study code:	ABX464-103
Version number:	3.0
Release date:	June 01st, 2020

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Study Phase	Phase IIb
Coordinating Investigator	***Prof. Severine Vermeire*** University Hospitals Leuven - campus Gasthuisberg Gastroenterology UZ Herestraat 49 - box 7003 08 3000 Leuven Belgium
Sponsor	**ABIVAX** 5 rue de la Baume 75008 Paris Tel: +33 (0) 1 53 83 08 41 Fax: +33 (0) 1 53 83 07 48
Date/Version	June 01st, 2020 / Version 3.0

CONTACTS

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Coordinating investigator	**Prof. Severine Vermeire** University Hospitals Leuven - campus Gasthuisberg Gastroenterology Herestraat 49 - box 7003 08 3000 Leuven - Belgium
Central Laboratory	**Eurofins Central Laboratory** Bergschot 71 4817 PA Breda - The Netherlands
Imaging Central Review	**Bioclinica** 72 Hammersmith Road, 6th Floor London, W14 8UD- United Kingdom
Study Conduct, Data management and Statistical Analysis	**IQVIA** 151-161 Boulevard Victor Hugo 93588 Saint Ouen Cedex - France
miRNA-124 determination	**Biogazelle** Technologiepark-Zwijnaarde 82, 9052 Gent - Belgique
Histopathology (RHI)	**Cerba Research (Histalim)** 126, rue Emile Baudot Le Millénaire – 34000 Montpellier -France
Pharmacokinetics	**Charles River (Bioanalyses)** ZI de Brais 1 Rue Graham Bell BP 40309 44605 Saint-Nazaire - France
Pharmacovigilance	**IntuVigilance Limited** Scotsbridge House, Scots Hill Rickmansworth WD3 3BB Hertfordshire, UK

INVESTIGATOR AGREEMENT PAGE

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

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

Investigator's Name: _____

Investigator's Signature: _____

Date: _____

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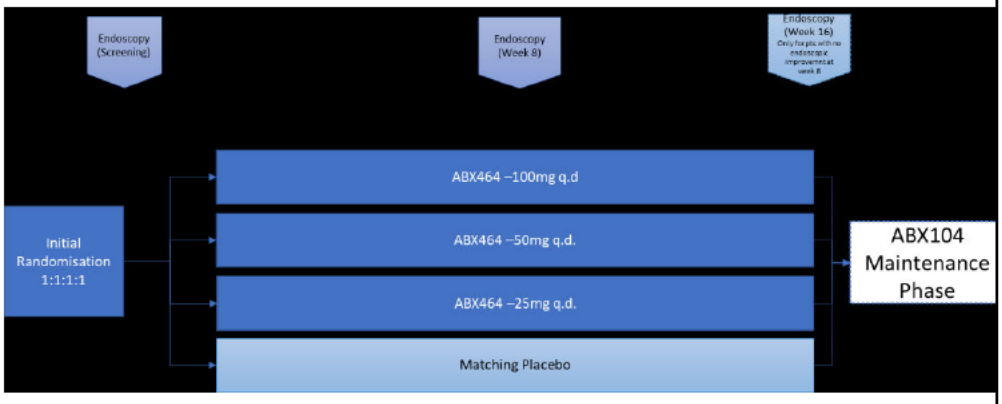
ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
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
CBC	Cap Binding Complex
CI	Confidence Interval
Cmax	peak plasma concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CRF	Case Report Form
CRP	C Reactive Protein
CTC-AE	Common Terminology Criteria for Adverse Events, version 5.0
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome
DBP	Diastolic Blood Pressure
DSMB	Data and Safety Monitoring Board
DSS	Dextran Sulfate Sodium
ECG	electrocardiogram
ECCO	European Crohn's and Colitis Organisation
EDTA	ethylenediaminetetraacetic acid
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GM	Geometric Mean
H	hours
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
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-22	Interleukine 22
IMP	Investigational Medicinal Product
JAK	Janus Kinase
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	minimum
miR	micro-RNA
mL	milliliter
mmHg	millimeters of mercury
NOAEL	No Observed Adverse Effect Level
MMS	Modified Mayo Score
o.d.	Once Daily
PCSA	potentially clinically significant abnormalities
PD	pharmacodynamics
PK	pharmacokinetics
pMMS	Partial Modified Mayo Score
PT	Preferred Term
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
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SF-36	Quality of Life Questionnaire
SmPC	Summary of Product Characteristics
SOC	system organ class
t1/2	terminal half-life
TB	Tuberculosis
TEAE	treatment emergent adverse event
tmax	time to peak plasma concentration
TMS	Total Mayo Score
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
ULN	Upper Limit Normal
Vd/F	volume of distribution
vs.	versus

SYNOPSIS

<table>
<tr><td colspan="2">Study n° ABX464-103 Clinical Phase IIb
Type of Study Safety, Efficacy, Dose-Ranging Study</td></tr>
<tr><td>Study title</td><td>A randomized, double blind, placebo controlled, parallel group, multiple dose, induction study to evaluate the safety, tolerability and optimal dose of ABX464 compared with placebo in patients with moderate to severe ulcerative colitis who have inadequate response, loss of response, or intolerance with at least one of the following agents: immunosuppressant treatment (i.e. azathioprine, 6-mercaptopurine, methotrexate), tumor necrosis factor alpha [TNF-α] inhibitors, vedolizumab, JAK inhibitors and/or corticosteroid treatment.</td></tr>
<tr><td>Short title</td><td>Phase IIb study of ABX464 in Moderate to Severe Active Ulcerative Colitis patients.</td></tr>
<tr><td>Investigators and study centers</td><td>Approximately 110 to 150 sites in Europe, Canada and the USA will participate in this study</td></tr>
<tr><td>Study Duration</td><td>Recruitment period: Q1 2019 – Q4 2020
Overall Study period: Q1 2019 – Q2 2021</td></tr>
<tr><td>Investigational medicinal product</td><td>ABX464 is a small molecule that binds the Cap Binding Complex (CBC), a protein complex sitting at the 5' ends of RNAs and that is involved in cellular RNA integrity (e.g. splicing). ABX464 does not affect RNA biogenesis from cellular genes. ABX464 enhances the splicing of a long non-coding RNA to up-regulate microRNA miR-124, which functions as a potent endogenous anti-inflammatory mediator. ABX464 has anti-inflammatory properties in Dextran Sulfate Sodium (DSS)and rheumatoid arthritis models. Administration of ABX464 has demonstrated clinical efficacy in moderate to severe Ulcerative Colitis (UC) patients. ABX464 was safe and well tolerated in approximately 200 volunteers and patients in phase I and II clinical trials.</td></tr>
<tr><td>Study Design and Methodology</td><td>This phase IIb study will evaluate the efficacy and the safety of 3 dose-levels of ABX464, administered daily in improving Modified Mayo Score (MMS) in patients with moderate to severe Ulcerative Colitis at Week 8.
Eligible patients will be randomized into 4 parallel intervention/treatment groups:
<table>
<tr><th></th><th>Intervention/treatment Active Arm</th></tr>
<tr><td>Group #1: 25mg qd</td><td>1 capsule of 25mg ABX464 + 1 capsule of Placebo</td></tr>
<tr><td>Group #2: 50mg qd</td><td>1 capsule of 50mg ABX464 + 1 capsule of Placebo</td></tr>
<tr><td>Group #3: 100mg qd</td><td>2 capsules of 50mg ABX464</td></tr>
<tr><td>Group #4: Placebo</td><td>2 capsules of Placebo</td></tr>
</table>
The study design is presented below:


At Week 16, regardless of their clinical/symptomatic response and the actual treatment/dose received, patients willing to continue the study treatment and eligible for enrollment will roll over in an Open Label Extension study (ABX464-104). In this extension study, all patients will be dosed with ABX464 50mg q.d. ABX464-104 is a separate clinical protocol subject to health authorities and ethics committee approvals.
In the present induction study (ABX464-103), randomization will be stratified according to the following stratification factors:
1) US versus non-US patients
2) Patients without previous exposure to biological drugs or JAK inhibitors versus</td></tr>
</table>

Study n° ABX464-103	**Clinical Phase** IIb **Type of Study** Safety, Efficacy, Dose-Ranging Study
	patients with previous exposure to biological drugs or JAK inhibitors. The proportion of patients with previous exposure to biologics or JAK inhibitors will be limited to 60%, including a maximal proportion of patients with previous treatment with vedolizumab of 20%. The maximal proportion of patients with previous exposure with JAK inhibitors will be limited to 10%. Patients will be treated for 16 Weeks in this induction study. All endoscopies (videos) will be centrally reviewed. E-Diaries will be used to collect frequency of stools, rectal bleedings, number of capsules taken and the intake time. From Day 1 onwards, randomized patients will be seen at the investigational site on a regular basis (cf. flow-chart). Flexible sigmoidoscopy with rectal and sigmoidal (if the sigmoidal is inflamed) biopsies will be performed at screening, at Day 57 +/- 4 days (week 8) and at Day 113 +/- 4 days (week16). The Day 113 measurement will only be performed if patient does not experience endoscopic improvement at Day 57 (i.e.: endoscopy sub-score of 2 or 3). From Week 8 onwards, in the event of clinical progression of the disease defined as at least a 2-point increase from the screening in partial Modified Mayo Score (pMMS) with a Modified Mayo Score ≥ 4 confirmed by an endoscopy sub score of 2 points or higher, the patient will exit definitively the study. Approximately 244 patients will be randomized in this study (i.e. 61 patients per study treatment arm).
Study Objectives	**Primary Objective** The primary objective of the study is to determine an optimal ABX464 dose to be used in moderate to severe active ulcerative colitis patients who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab, JAK inhibitors and/or corticosteroids by comparing the mean change from baseline in the MMS at week 8 between each ABX464 group and placebo. **Secondary Objectives** The secondary objectives are: ▪ To evaluate the effect of the different dose groups of ABX464 on Modified Mayo Score at Week 16 (if available) and on partial Modified Mayo Score at every study visit versus placebo. ▪ To evaluate the global effect of ABX464 on Modified Mayo Score at Week 8 and Week 16 (if available) and on partial Modified Mayo Score at every study visit versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on clinical remission at Week 8 and at Week 16 (if available) versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on clinical response at week 8 and at Week 16 (if available) versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on endoscopic improvement and endoscopic remission, by segment, at Week 8 and Week 16 (if available) versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on mucosal healing, at Week 8 and Week 16 (if available) versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on stool and rectal bleeding frequency at every study visit versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on fecal calprotectin and CRP levels at Week 8 and Week 16 versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on miR-124 expression in tissue (RNA later) at Week 8 and Week 16 (if available) and in total blood at every timepoint versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 versus placebo on the rectal/sigmoidal infiltrates using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at Week 8 and Week 16 (if available) versus placebo.

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	▪ To evaluate the effect of the different dose groups of ABX464 on Quality of Life (QoL) measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 8 and Week 16 versus placebo. ▪ To evaluate the effect of the different dose groups of ABX464 on IL-6, TNFα, IL-1b, IL-10 plasma concentrations at every timepoint versus placebo. ▪ To assess the pharmacokinetics of the ABX464 and its main active metabolite ABX464-N-Glu after oral administration of different daily doses of ABX464 using population approach. ▪ To evaluate the safety profile of the different dose groups of ABX464 versus placebo.
Study Endpoints	**Primary Endpoint:** ▪ Reduction from baseline in Modified Mayo Score at Week 8. **Secondary Endpoints:** The secondary endpoints are: ▪ Number and rate of patients in clinical remission at Week 8, per each intervention/treatment group. Clinical remission, based on the Mayo Scoring system, is defined as stool frequency subscore = 0 or 1 and rectal bleeding subscore = 0 and endoscopy subscore = 0 or 1 (modified to exclude friability). ▪ Combined number and rate of patients in clinical remission at Week 8 and at Week 16, per each intervention/treatment group. ▪ Number and rate of patients with clinical response at Week 8 and Week 16 per intervention/treatment group. Clinical Response is defined as a reduction in Mayo Score of at least 2 points and greater than or equal to 30 percent from baseline with an accompanying decrease in rectal bleeding sub-score of greater than or equal to 1 point or absolute rectal bleeding sub-score of less than or equal to 1 point. ▪ Number and rate of patients with endoscopic improvement, by segment, and number and rate of patients with endoscopic remission, by segment, at Week 8 and at Week 16 (if available) per intervention/treatment group. Endoscopic improvement is defined as a Mayo endoscopic sub score of ≤1 (excluding friability) and endoscopic remission defined as sub score of 0. ▪ Number and rate of patients with mucosal healing. Mucosal healing is defined as both endoscopic remission and histological remission (Geboes score < 2.0) ▪ Reduction relative to baseline in stool and rectal bleeding frequency at every study visit by ABX464 dose group and versus placebo. ▪ Reduction relative to baseline in partial Modified Mayo Score at every study visit and Modified Mayo Score at Week 16 (if available) by ABX464 dose group and versus placebo. ▪ Reduction relative to baseline in fecal calprotectin and CRP levels at Week 8 and Week 16 by intervention/treatment group. ▪ Change relative to baseline in miRNA-124 expression in rectal/sigmoidal biopsies at Week 8 and Week 16 and in total blood at every timepoints by intervention/treatment group. ▪ The scores and changes from baseline in IBDQ at Week 8 and Week 16 per intervention treatment group. ▪ Reduction relative to baseline of infiltrate/histopathology (rectal/sigmoidal biopsies) using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at Week 8 and Week 16 (if available) per intervention/treatment group. ▪ Change relative to baseline in IL-6, TNFα, IL-1b, IL-10 plasma concentrations at every timepoints by intervention/treatment group. ▪ Serum concentration of ABX464 and N-Glu ABX464 according to dose group. ▪ Number and rate of all adverse events, causally-related adverse events, all SAE and causally-related SAEs classified by severity per intervention/treatment group. ▪ Incidence of treatment-emergent serious adverse event per intervention/treatment group. ▪ Incidence of adverse events leading to investigational medicinal product discontinuation per intervention/treatment group.

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	▪ The number of clinically-significant laboratory abnormalities per intervention/treatment group.
Main Selection Criteria	**Inclusion criteria:** **A patient will be eligible to participate in this study if ALL the following criteria are met:** ▪ Men or women age 18 - 75 years; ▪ Diagnosis of moderate to severe active UC (including ulcerative proctitis if proximal extension of disease occurs beyond 10 cm) confirmed by endoscopy and histology at least 12 Weeks prior to screening visit. Moderate to severe active UC defined by Modified Mayo Score (MMS) of 5 to 9 inclusive (on a scale of 0-9). Moderate to severe active UC should be confirmed at screening visit with a centrally read endoscopy sub-score of at least 2 (on a scale of 0-3); ▪ Patients having either a documented inadequate response, no response, a loss of response, or an intolerance (defined as the occurrence of at least one Adverse Reaction leading to treatment discontinuation) to either immunosuppressant treatment (i.e., azathioprine, 6-mercaptopurine, methotrexate), tumor necrosis factor [TNF] inhibitors, vedolizumab, JAK inhibitors and/or corticosteroid treatment. Inadequate response, no response, loss of response is defined as: o Active disease or relapse in spite of thiopurines or methotrexate given at an appropriate dose for at least 3 months (i.e. azathioprine 2–2.5 mg/kg/day or mercaptopurine 1–1.5 mg/kg/day in the absence of leukopenia), and/or o Active disease despite corticosteroids treatment (prednisolone up to 0.75 mg/kg/day) over a period of 4 Weeks, and/or o Active disease or relapse in spite of adequate treatment (as defined in the SmPC) with tumor necrosis factor [TNF] inhibitors or vedolizumab, and/or o Active disease or relapse in spite of adequate treatment with JAK inhibitors over a period of at least 6 Weeks. ▪ Patients receiving oral corticosteroids must have been on a stable dose of prednisone or prednisone equivalent (≤20 mg/day) or on beclomethasone diproprionate (≤5mg/day) or on budesonide MMX (≤9 mg/day) for at least 2 Weeks prior to the screening visit; ▪ Topical corticosteroids and topical 5-aminosalicylic acid preparations must have been withdrawn at least 2 Weeks prior to the screening visit; ▪ Patients who are on oral 5-aminosalicylic acid must have been on a stable dose for at least 4 Weeks prior to the screening visit; ▪ Patients who are receiving immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate needed to be on a stable dose for at least 4 Weeks prior to screening visit. Patients taking methotrexate also are advised to take folic acid 1 mg/day (or equivalent) supplementation if there is no contraindication; ▪ Patients on probiotics (e.g., Culturelle® [Lactobacillus GG, i-Health, Inc.], Saccharomyces boulardii) must be on stable doses for at least 2 Weeks prior to the screening visit; ▪ Patients on antidiarrheals (e.g., loperamide, diphenoxylate with atropine) must be on stable doses for at least 2 Weeks prior to the screening visit; ▪ Patients who have received tumor necrosis factor [TNF] inhibitors, vedolizumab or other biologics must have discontinued therapy at least 8 Weeks prior to the screening visit due to lack or insufficient efficacy or intolerance; ▪ Patients previously treated with cyclosporine, tacrolimus or JAK inhibitors must have discontinued therapy at least 4 Weeks prior to the screening visit due to lack or insufficient efficacy or intolerance; ▪ Patients previously treated with tube feeding, defined formula diets, or parenteral alimentation/nutrition must have discontinued treatment 3 Weeks before the screening visit and must be able to take, orally, appropriate amount of food (calories) and liquids to maintain body weight; ▪ Patients with surveillance colonoscopy defined as per ECCO guidelines; ▪ Patients with the following hematological and biochemical laboratory parameters obtained at screening: o Hemoglobin > 9.0 g dL^{-1};

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- Absolute neutrophil count ≥ 750 mm^{-3};
- Platelets ≥ 100,000 mm^{-3};
- Total serum creatinine ≤ 1.3 x ULN (upper limit of normal);
- Creatinine clearance > 90 mL min^{-1} by the Cockcroft-Gault equation within 60 days prior to baseline;
- Total serum bilirubin < 1.5 x ULN;
- Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 2 x ULN;

- 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 at the screening visit 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 after end of study or early termination. Contraception should be in place at least 2 Weeks prior to study participation. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (WOCBP) will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception aiming at inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the Patient. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with an infrequent or irregular menstrual cycle. Female and male patients must not be planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male participants should use condoms and not donate sperm as long as contraception is required.

Exclusion Criteria:

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

- Patients with Crohn's Disease (CD) or presence or history of fistula, indeterminate colitis (IC), infectious/ischemic colitis or microscopic colitis (lymphocytic and collagenous colitis);
- History of toxic megacolon, abdominal abscess, symptomatic colonic stricture or stoma; history or imminent colectomy, colonic malignancy;
- History or current evidence of colonic dysplasia or adenomatous colonic polyps. Patient with severe gastrointestinal complications; e.g., short bowel syndromes, recent or planned bowel surgery, Ileostomy and/or colostomy, recent bowel perforation;
- History of more than one episode of herpes zoster or a history (single episode) of disseminated zoster;
- Patients with active infections at screening such as infected abdominal abscess, Clostridium difficile (stool antigen and toxin required), CMV [(positive immunoglobulin M (IgM)], TB and recent infectious hospitalization;
- Patients previously treated with ABX464;
- Acute, chronic or history of clinically relevant pulmonary, cardiovascular, hepatic, pancreatic or renal functional abnormality, encephalopathy, neuropathy or unstable CNS pathology such as seizure disorder, angina or cardiac arrhythmias, active malignancy or any other clinically significant medical problems as determined by physical examination and/or laboratory screening tests and/or medical history;
- Acute, chronic or history of immunodeficiency or autoimmune disease;
- History of malignancy excluding patients considered cured (5 years disease free survivors);
- Serious illness requiring systemic treatment and/or hospitalization within 3 Weeks prior to baseline;
- Pregnant or breast-feeding women;

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	▪ Illicit drug or alcohol abuse or dependence; ▪ Patients who received live vaccine 30 days or fewer before first dose of study treatment and/or who's planning to receive such a vaccine during the study duration; ▪ Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer and during the study; ▪ Any condition, which in the opinion of the investigator, could compromise the patient's safety or adherence to the study protocol.
Medications	**Allowed Concomitant Medications:** ▪ Corticosteroids at stable dose of prednisone or prednisone equivalent ≤20 mg/day; beclomethasone diproprionate (≤5mg/day) or budesonide MMX (≤9 mg/day); ▪ Oral 5-aminosalicylic acid at stable dose; ▪ Immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate at stable dose; ▪ Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) at stable dose. **Prohibited Concomitant Medications:** ▪ Tumor necrosis factor [TNF] inhibitors, vedolizumab or others biologic therapies with a wash-out period of at least 8 Weeks prior to the screening visit; ▪ JAK inhibitors with a wash-out period of at least 4 Weeks prior to the screening visit; ▪ Topical corticosteroids and topical 5-aminosalicylic acid preparations with a wash-out period of at least 2 Weeks prior to the screening visit; ▪ Cyclosporine and tacrolimus with a wash-out period of at least 4 Weeks prior to the screening visit; ▪ Vaccination with live components during the study and up to 8 Weeks after the last dosing; ▪ Drugs that could interact with ABX464 should be avoided especially the CYP1A2 substrates (cf. Appendix #1). The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (Clozapine, theophylline, ropinirol, warfarin and methadone). In case of concomitant treatment with ondansetron the maximal daily dose must be limited to 8 mg; ▪ Drugs that inhibit or induce CYP1A2 (cf. Appendix #1). ▪ Drugs that inhibit UGTIA9 activity and inhibitors of OATP1B1/1B3 transporters (cf. Appendix #1). ▪ Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer and during the study.
Premature trial discontinuation	Patient's premature trial discontinuation could occur for the following reasons: ▪ Investigator's decision; patient that 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 off from study treatment; ▪ An Adverse Event or an intercurrent condition that preclude continuation of treatment; o 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%).

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	▪ Worsening of the UC defined, from Week 8 onwards, 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; ▪ Major protocol violation; ▪ Patient's decision; ▪ Withdrawal of consent.
Patient Follow-up	On Day 113 +/- 4 days, eligible patients willing to continue study treatment will be able to take part in an Open Label Extension study (ABX464-104). In this extension study, all patients will be dosed with ABX464 50mg QD. ABX464-104 maintenance study is a separate clinical study requiring health authorities and ethics committees' approvals.
Data Safety Monitoring Board (DSMB)	A Data Safety Monitoring Board with expertise and experience in the management in UC will review the safety of the trial every two months during the entire study period. The DSMB will oversee the adequate balance of baseline characteristics (gender, disease duration, fecal calprotectin level, tobacco use) among the treatment groups. In addition, DSMB will be review all potential causally-related Serious Adverse Events within 7 days of the initial report.
Sample Size calculation	The primary endpoint is the change in the Modified Mayo Score (MMS) from Baseline to Week 8. The primary endpoint will be compared between subjects who received ABX464 and placebo for each ABX464 dose group separately. For sample size calculation the following assumptions were made: • mean reduction in MMS (ABX464): 2.5 • mean reduction in MMS (placebo): 1.0 • pooled standard deviation of reduction in MMS: 2.1 • Type 1 error: 5% two-sided. • Treatment testing to use a sequential, gate-keeping strategy, where treatments will be tested in the following order: ABX464 50mg vs. placebo, ABX464 100mg vs. placebo, ABX464 25mg vs. placebo. Subsequent tests will only be performed only if prior test(s) are significant ($p<0.05$). • >90% power • Two-sample t-test • 5% dropout rate prior to Week 8 MMS assessment (all treatment arms) • 1:1:1:1 (ABX464 100mg: ABX464 50mg: ABX464 25mg: placebo) study treatment allocation ratio. If the above assumptions hold true, then a total sample size of 232 subjects will be required to be randomized (58 subjects randomized to each study treatment arm). Due to the SARS Cov-2 pandemic the drop-out rate of the study is expected to be somewhat higher than originally estimated. Therefore, an additional 12 subjects are planned to be recruited in the study, leading to an overall sample size of 244 patients (61 subjects randomized to each study treatment arm).
Statistical Methods	Analysis of efficacy data will be carried out using the Full Analysis Set. The primary efficacy endpoint of the study is the change in the Modified Mayo Score (MMS) from Baseline to Week 8. This change will be compared between subjects who received ABX464 and placebo for each ABX464 treatment arm separately using an ANCOVA model adjusting for randomized study treatment arm, US vs non-US, previous biological or JAK inhibitors treatment use (i.e. randomization strata), and baseline MMS. The dose testing will commence with comparing the ABX464 50mg dose with placebo. If this is significant at a 5% two-sided level (i.e. $p<0.05$) a comparison against placebo will be carried out at the ABX464 100mg dose. Again, if significance at a 5% level for this test is observed the procedure will be repeated at the ABX464 25mg dose. In this closed procedure no adjustment for multiple comparison is needed. Should the data warrant it, testing between doses may also be conducted. In addition, descriptive statistics will be presented by treatment arm for all secondary efficacy variables for each measurement timepoint. These statistics include:

Study n° ABX464-103	**Clinical Phase** IIb **Type of Study** Safety, Efficacy, Dose-Ranging Study
	• Continuous variables: mean, standard deviation, minimum and maximum, 95% Confidence intervals for the mean, median and quartiles will be presented. • Categorical variables: counts, rates and 95% confidence intervals for the rates will be calculated. In addition to descriptive statistics, the following analyses will also be carried out for the variables indicated below: • The global (combined) ABX464 treatment effect vs. placebo in the change from Baseline in Modified Mayo Score at Week 8. • Mixed model analysis of covariance will be conducted for the following measurements: o The change from baseline in miRNA-124 levels in total blood (PAXgene®) at Week 1, Week 4, Week 8 and Week 16 and in tissue (RNA later) at Week 8 and Week 16 (if available). o The change from baseline in fecal calprotectin and CRP levels at Week 8 and Week 16. o The change from screening in the histopathology/infiltrate (rectal/sigmoidal biopsies) assessed by the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at Week 8 and Week 16 (if available). o The change from screening in partial Modified Mayo scores during the study. In this model, treatments and stratum will be fixed effects, subject will be random effect and baseline values of the respective measurements will be covariates. Other explanatory variables will also be allowed to be included in the model. To normalize eventual skewed distributions, transformation of the data will also be considered. Study treatment groups will be compared within this model framework. All p-values will be interpreted in a descriptive manner. The following subgroups will be analyzed: • Gender • Age • Country • US vs non-US • Baseline MMS • With/without previous biological or JAK inhibitors treatment • Week 16 ABX464-NGlu AUC_{0-12} level above/below 7 000 h*ng/mL (vs. placebo). • Concomitant UC medications. ***Safety:*** Analysis of safety will be performed on the safety data set consisting in all patients who received at least one dose of ABX464 or placebo in the study. The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the "CTC-AE" (Version 5.0) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and potentially clinically significant abnormalities (PCSAs) as determined upon investigator considerations. Adverse events will be tabulated (counts and percentages) by dose groups. All adverse events will be listed and the data will be tabulated by body system/organ class. Adverse event tabulations will include all treatment emergent adverse events, which will be further classified by severity, and relationship to treatment. Clinical laboratory parameters, vital signs, ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). The number of patients with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables by dose groups. ***Population Pharmacokinetics:*** Blood samples will be collected in all patients for PK assessment. Sampling will be performed on Day 1 and on the last day of study treatment. Two elementary sampling designs will be used to limit the number of samples in each patient:

Study n° ABX464-103	**Clinical Phase** IIb **Type of Study** Safety, Efficacy, Dose-Ranging Study

	• Group 1:
	  ○ Day 1: 0.5, 1.5, 3h (and 6 h and/or 10 h if possible)
	  ○ Last day (Day 113): predose, 1, 2, 4h and if possible 48h (Day 115). D115 will only be taken if the subject is not transitioning to the ABX464-104 study.
	• Group 2:
	  ○ Day 1: 1, 2, 4h (and 8 h and/or 12 h if possible)
	  ○ Last day (Day 113): predose, 0.5, 1.5, 3h and if possible 48h (Day 115). D115 will only be taken if the subject is not transitioning to the ABX464-104 study.
	In addition to these sampling time points, predose concentrations will be collected at the study visit day 8, 29, 85. Patient data will be pooled with data obtained in previous clinical studies in order to build a population pharmacokinetic models for ABX464 and its metabolite.

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] in the hope that the etiology of ulcerative colitis will be elucidated and a cure developed.

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.

In-vitro assays revealed that both ABX464 and its primary metabolite, ABX464-N-Glu, induced a significant increase in miR-124 expression in PBMCs in a dose dependent manner.

Results support the hypothesis that ABX464 and ABX464-N-Glu bind directly to Cap-Binding Complex without interfering with cap binding function. Both molecules selectively modulate RNA biogenesis by direct binding to the cellular CBC, leading to an increased expression of miR-124 while not affecting other cellular RNAs. In inflammatory conditions, miR-124 expression is associated with the down regulation of a variety of pro-inflammatory cytokines/mediators and can induce an anti-inflammatory effect. Literature reports indicate that miR-124 appears to regulate the expression of signal transducer and activator of transcription 3 (STAT3), MCP-1, IL6-R and TNFα. In the DSS mouse model, a reduction in MCP-1, IL6 and TNFα was observed following ABX464 treatment. MCP-1 is a direct target of miR-124. ABX464 and ABX464-N-Glu up-regulate the production of miR-124 by binding to the CBC.

ABX464 and ABX464-N-Glu have shown strong anti-inflammatory effects in vivo, in the inflammatory bowel disease (IBD) mouse dextran sulfate sodium (DSS)-model. Results from in vivo studies using the DSS-induced mouse model showed that DSS-induced weight loss, an established symptom of intestinal injury. This weight loss was significantly reduced in mice receiving ABX464. The model showed that ABX464 had no detectable effect on the expression profile of cytokines and chemokine signaling pathways in the absence of DSS exposure. However, ABX464 compensated for most of the expression differences induced by DSS exposure, suggesting that it can restore normal transcription in this model. ABX464-N-Glu demonstrated a similar effect as ABX464 regarding the dampening of body weight loss in DSS-induced colitis.

This mode of action is unlike any currently approved drug. Because of its action on this single splicing event, leading to an increase in miR124, ABX464 potentially has broad utility in a variety of diseases.

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.

Clinical studies have been completed with ABX464 in healthy volunteers (2 studies) and patients with HIV infection (3 studies, including one study with a healthy volunteer cohort).

Completed and ongoing studies with ABX464 in inflammation are:

Ulcerative colitis

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

Rheumatoid arthritis

- Phase 2a program with a 12-week induction (ABX464-301; ongoing) and 52-week maintenance (ABX464-302; ongoing) studies

1.2.2. Investigational medicinal product description

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

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

1.2.3. Investigational medicinal product Mode of Action

ABX464 and ABX464-N-Glu bind the CBC (Cap Binding Complex), comprised of two proteins CBC20 and CBC80, within the cell nucleus. This binding leads to an increase in a single micro-RNA (miR124) expression by impacting the splicing of a single long non-coding RNA.

1.2.4. Rationale for the development of ABX464 in Ulcerative Colitis

In-Vitro assays

- *Modulation of miR-124 by ABX464*

Study ABX464PHA011 performed in humans PBMCs revealed that both ABX464 and its primary metabolite ABX464-N-Glu induced a significant increase in miR-124 expression. MiR-124 appears to regulate the expression of signal transducer and activator of transcription 3 (STAT3). MiR-124 has also been shown to be required for the protective role of nicotine in DSS colitis mice.

- *Bone Marrow Derived Macrophages – LPS Challenge*

Stimulation of BMDMs with LPS induced the expression of IL6, TNFα, and MCP1 (CCL2) but not that of IL10 (Figure 1B). The expressions of MCP1 and IL6 persisted for 48 h post LPS-stimulation, whereas TNF expression was down-regulated at 12 h (Figure 1B). Strikingly, ABX464-exposed BMDMs displayed an increased production of IL-10 at 12 and 24 h post LPS-stimulation but did not alter levels of the pro-inflammatory cytokines IL6 and TNFα (Figure 1B).

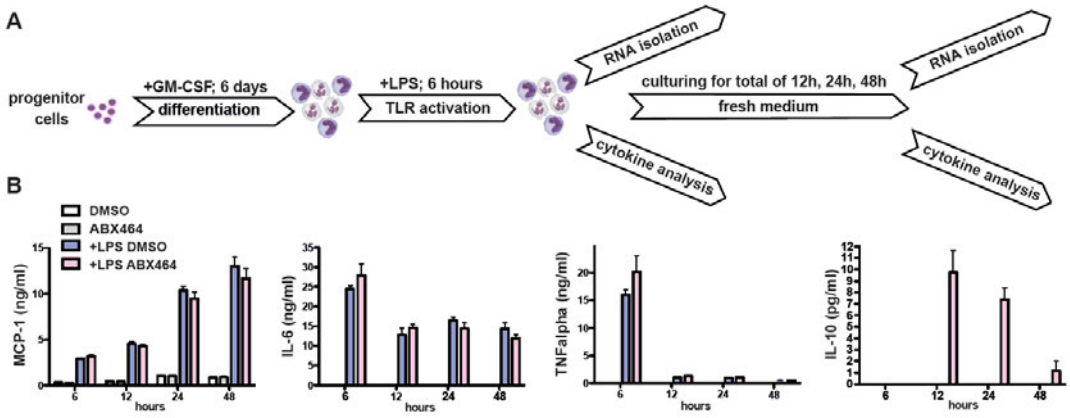


Figure 1. Effect of ABX464 on cytokine secretion **(A)** Bone marrow isolated cells were cultured for 6 days in the presence of GM-CSF (50ng/ml) to differentiate into macrophages. Cells were kept in culture for additional 3 days in the presence of ABX464 (5µM) or vehicle (DMSO) alone and for additional 6 hours stimulated with LPS (4µg/ml). Cells were then kept in normal medium for additional 42 hours. Cell aliquots for RNA isolation and supernatants were taken at time 6, 12, 24 and 48 hours. **(B)** Culture supernatants of the indicated cell cultures were analyzed by CBA for the content of MCP-1, IL-6, TNFalpha and IL-10.

In-Vivo assays

- *DSS mice model*

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

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

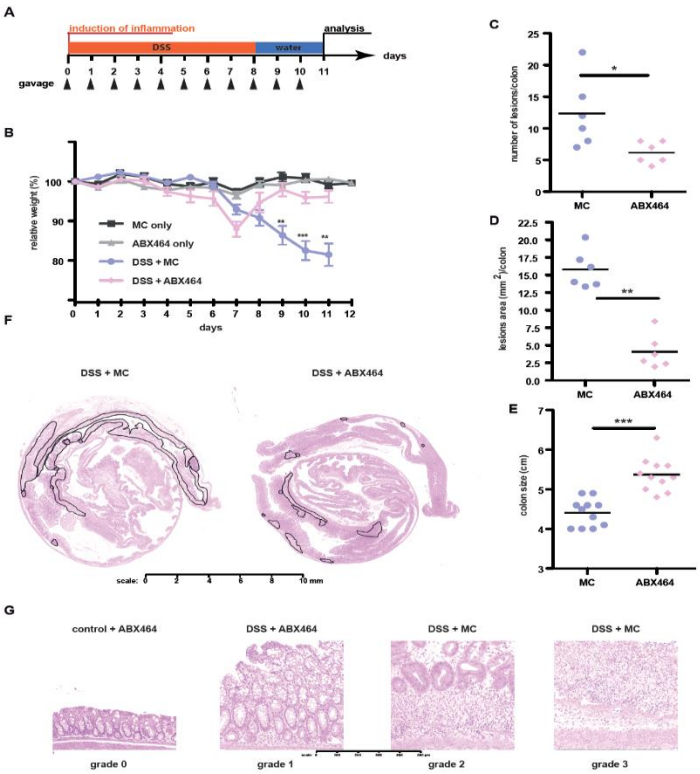


Figure 2: ABX464 treatment suppresses disease severity in DSS-induced colitis. **(A)** C57BL/6 mice (n=12 each cohort) Patiented to the DSS colitis protocol shown received orally once a day ABX464 (50 mg/kg) in methylcellulose or methylcellulose only through gavage. **(B)** Weight development in ABX464 and methycellulose (MC) only treated mice during DSS-induced colitis. Control cohorts included mice not exposed to DSS. **(C, D, E)** At the end of the protocol described in A mice were sacrificed and colons were analyzed by histology for colitis severity including number of lesion (C), lesion size (D) and colon size (E). **(F)** Representative images of hematoxylin and eosin staining of paraffin-embedded colon sections prepared as “Swiss rolls”. Single lesions are delimited by black lines. **(G)** Representative images of lesions with different pathological grade according to Hao et al. Grade 1: Immune cell infiltration in lamina propria (LP); intact epithelial barrier and GI structure. Grade 2: Immune cell infiltration in LP; crypt distorsion or loss; gobelet cell loss; intact, but abnormal epithelial barrier. Grade 3: Immune cell infiltration in LP and submucosa; epithelial barrier loss and ulceration/necrosis.

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

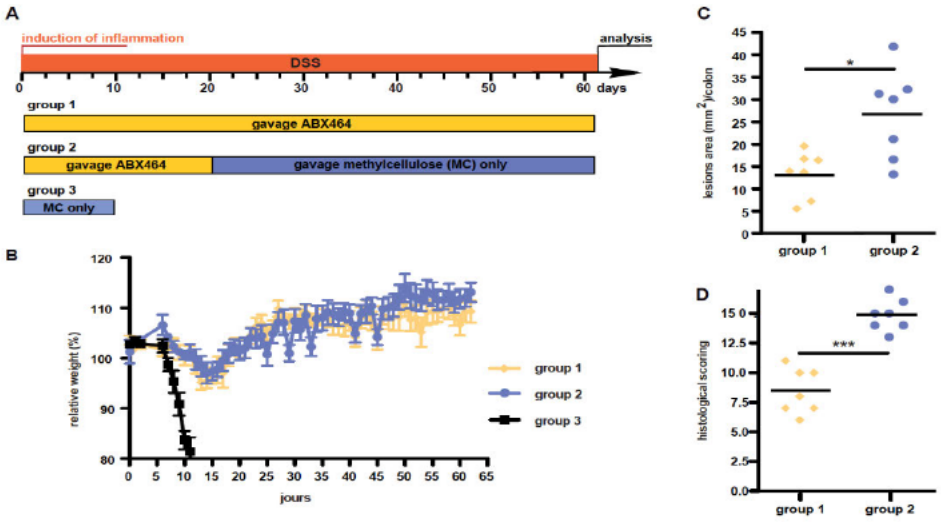


Figure 3: The protective effect of ABX464 is maintained in mice during continuous DSS-treatment. **(A)** C57BL/6 mice (n=8 each cohort) were challenged with DSS for 63 days. Mice received orally once a day ABX464 in methylcellulose during the whole protocol (group 1) or only for the first 20 days followed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

In humans, ABX464 is rapidly metabolized into one main metabolite, ABX464-N-Glucuronide. Thus, ABIVAX studied in the same DSS-mice model the efficacy of the ABX464-N-Glucuronide. Alike ABX464, ABX464-NGlc (40 mg/kg) protects mice from DSS-induced weight loss (Figure 4). This finding has substantial implications in light of treating inflammatory ulcerative colitis (UC) disease since studies in healthy patients demonstrated that:

- ABX464-N-Glu's Cmax was approximately 160-fold higher than those of ABX464 and had a much longer t1/2 (90 to 110 hours) than the parent compound (2-3 hours), resulting in a > 1000-fold difference in AUC between the 2 compounds.
- The markedly higher plasma concentrations of ABX464-N-Glu, and its ability to protect mice from DSS-induced colitis, may allow the use of lower concentrations of the parent compound ABX464 for longer period in UC patients.

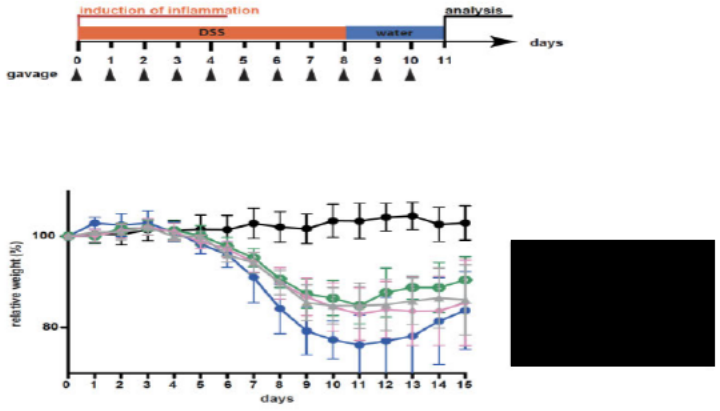


Figure 4: ABX464-N-Glu treatment suppresses disease severity in DSS-induced colitis. **(A)** C57BL/6 mice (n=8 each cohort) Patiented to the DSS colitis protocol shown received orally once a day ABX464 40 mg/kg (464-40 DSS), 10 mg/kg (464-10 DSS) or ABX464-NGlc 40 mg/kg (Glu40 DSS) in methylcellulose or methylcellulose only (MC DSS) through gavage. **(B)** Weight development in ABX464 ABX464-NGlc and methylcellulose (MC DSS) only treated mice during DSS-induced colitis. Control cohorts included mice not exposed to DSS (MC H2O).

Taken together, these *in-vivo* studies demonstrated the potency of the drug candidate ABX464 to dampen intestinal inflammation in DSS-treated mice. Through this anti-inflammatory effect, ABX464 might be able to modulate important disease parameters in both HIV and inflammatory ulcerative colitis

(UC) disease because it demonstrates long-lasting control of the HIV-virus in humanized mice as well as the critical features of DSS-induced colitis.

1.2.5.Preclinical data of ABX464

1.2.5.1. Non-clinical background information

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

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

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

[redacted]

In minipigs the main adverse finding was [redacted] observed at dose levels of [redacted]mg/kg and above. The liver lesions observed in the single animal administered [redacted]mg/kg od, were not considered adverse. Based on this observation, the NOAEL is [redacted]mg/kg od.

No signs of hepatotoxicity have been observed in any of the patients treated with ABX464 in the previously conducted or on-going clinical trials. ABIVAX and its clinical experts consider that patients treated with ABX464 are not at increased risk of developing a drug-induced hepatotoxicity.

A specific liver function monitoring plan has been implemented in the current clinical study.

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

1.2.5.2. Previous clinical experience with ABX464

The effect of ABX464 in humans has been assessed in 5 completed clinical studies in healthy volunteers and in patients with HIV as well as in 1 completed study in patients with UC (ABX464-101). In addition, there is efficacy and safety data available from an interim analysis of the longer-term maintenance Study ABX464-102 in UC. Two further studies in UC (ABX464-103; ABX464-104) and 2 studies in RA (ABX464-301; ABX464-302) are ongoing. As of October 31, 2019, 211 subjects have received single doses (25 to 200 mg) of ABX464, or repeated doses (50 to 150 mg) up to a maximum duration approaching 2 years. An additional 18 subjects have received ABX464 or placebo in ongoing blinded studies.

ABX464 was rapidly absorbed and metabolised into ABX464-N-Glu within about 1 hour of treatment whatever the dose. After repeated administrations of ABX464, an initial decrease in ABX464 AUC was observed until steady state was reached after 4 weeks of treatment. Exposure to ABX464-N-Glu was much higher than to ABX464 in all patients. Food significantly increased ABX464 exposure, at least 2.8-fold.3.

Overall, the safety profile of ABX464 is acceptable; 8 serious AEs have been reported with ABX464, which were all considered not related to the investigational product. The most frequently reported AEs were nausea, vomiting and headache which were of mild to moderate intensity, occurring after treatment onset and transient in nature. The anticipated ABX464 adverse events are: Nausea, Vomiting, Abdominal pain upper, Abdominal pain, Diarrhea and Headache

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

1.3. Rationale for the clinical study and study design

A Phase IIa 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 = 33.0%)

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

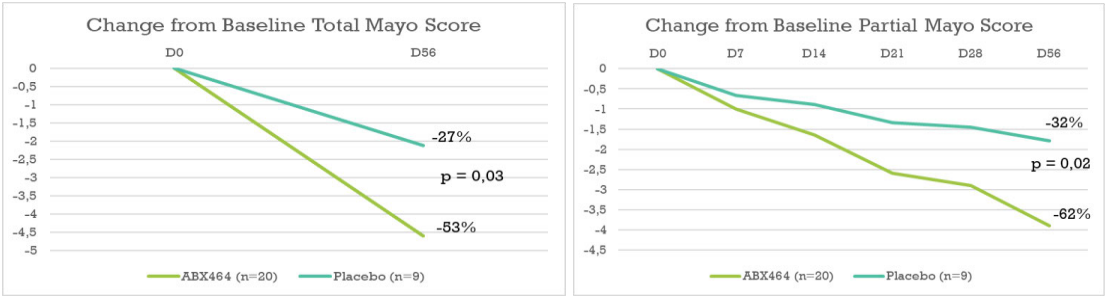


Figure 5: Mean change in Total and Partial Mayo in ABX464-101 study

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

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

Clinical remissions obtained at the end of the induction study were durable and the rates further improved during the maintenance phase, as additional subjects achieved clinical remission during 12 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 determine an optimal ABX464 dose to be used in moderate to severe active ulcerative colitis patients who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab, JAK inhibitors and/or corticosteroids by comparing the mean change from baseline in the MMS at week 8 between each ABX464 group and placebo.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the effect of the different dose groups of ABX464 on Modified Mayo Score at Week 16 (if available) and on partial Modified Mayo Score at every study visit versus placebo.
- To evaluate the global effect of ABX464 on Modified Mayo Score at Week 8 and Week 16 (if available) and on partial Modified Mayo Score at every study visit versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on clinical remission at Week 8 and at Week 16 (if available) versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on clinical response at week 8 and at Week 16 (if available) versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on endoscopic improvement and endoscopic remission, by segment, at Week 8 and Week 16 (if available) versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on mucosal healing, at Week 8 and Week 16 (if available) versus placebo
- To evaluate the effect of the different dose groups of ABX464 on stool and rectal bleeding frequency at every study visit versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on fecal calprotectin and CRP levels at Week 8 and Week 16 versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on miR-124 expression in tissue (RNA later) at Week 8 and Week 16 (if available) and in total blood at every timepoint versus placebo.
- To evaluate the effect of the different dose groups of ABX464 versus placebo on the rectal/sigmoidal infiltrates using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at Week 8 and Week 16 (if available) versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on Quality of Life (QoL) measured by the IBDQ at Week 8 and Week 16 versus placebo.
- To evaluate the effect of the different dose groups of ABX464 on IL-6, TNFα, IL-1b, IL-10 plasma concentrations at every timepoint versus placebo.
- To assess the pharmacokinetics of the ABX464 and its main active metabolite ABX464-N-Glu after oral administration of different daily doses of ABX464 using population approach.
- To evaluate the safety profile of the different dose groups of ABX464 versus placebo.

2.3. Primary Endpoint

The primary endpoint is the reduction from baseline in Modified Mayo Score at Week 8.

2.4. Secondary Endpoints

The secondary endpoints of this study are:

- Number and rate of patients in clinical remission at Week 8, per each intervention/treatment group. Clinical remission, based on the Mayo Scoring system, is defined as stool frequency subscore = 0 or 1 and rectal bleeding subscore = 0 and endoscopy subscore = 0 or 1 (modified to exclude friability).

- Combined number and rate of patients in clinical remission at Week 8 and at Week 16, per each intervention/treatment group.
- Number and rate of patients with clinical response at Week 8 and Week 16 per intervention/treatment group. Clinical Response is defined as a reduction in Mayo Score of at least 2 points and greater than or equal to 30 percent from baseline with an accompanying decrease in rectal bleeding sub-score of greater than or equal to 1 point or absolute rectal bleeding sub-score of less than or equal to 1 point.
- Number and rate of patients with endoscopic improvement, by segment, and number and rate of patients with endoscopic remission, by segment, at Week 8 and at Week 16 (if available) per intervention/treatment group. Endoscopic improvement is defined as a Mayo endoscopic sub score of ≤1 (excluding friability) and endoscopic remission defined as sub score of 0.
- Number and rate of patients with mucosal healing. Mucosal healing is defined as both endoscopic remission and histological remission (Geboes score < 2.0).
- Reduction relative to baseline in stool and rectal bleeding frequency at every study visit by ABX464 dose group and versus placebo.
- Reduction relative to baseline in partial Modified Mayo Score at every study visit and Modified Mayo Score at Week 16 (if available) by ABX464 dose group and versus placebo.
- Reduction relative to baseline in fecal calprotectin and CRP levels at Week 8 and Week 16 by intervention/treatment group.
- Change relative to baseline in miRNA-124 expression in rectal/sigmoidal biopsies at Week 8 and Week 16 (if available) and in total blood at every timepoints by intervention/treatment group.
- The scores and changes from baseline in IBDQ at Week 8 and Week 16 per intervention treatment group.
- Reduction relative to baseline of infiltrate/histopathology (rectal/sigmoidal biopsies) using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at Week 8 and Week 16 (if available) per intervention/treatment group.
- Change relative to baseline in IL-6, TNFα, IL-1b, IL-10 plasma concentrations at every timepoints by intervention/treatment group.
- Serum concentration of ABX464 and ABX464-N-Glu according to dose group.
- Number and rate of all adverse events, causally-related adverse events, all SAE and causally-related SAEs classified by severity per intervention/treatment group.
- The incidence of treatment-emergent serious adverse event per intervention/treatment group.
- The incidence of adverse events leading to investigational medicinal product discontinuation per intervention/treatment group.
- The number of clinically-significant laboratory abnormalities per intervention/treatment group.

3. INVESTIGATIONAL PLAN

3.1. Study design

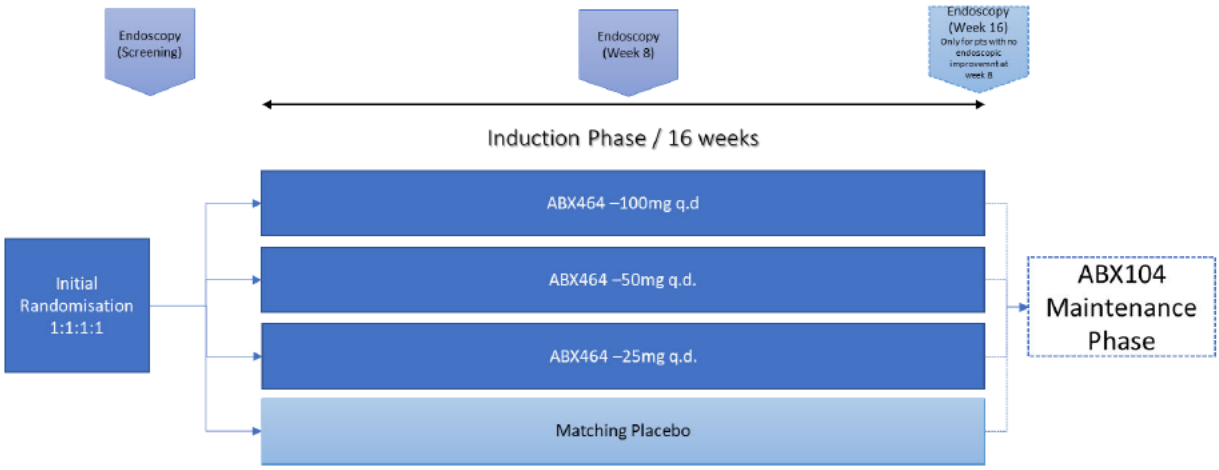
3.1.1.Design and methodology

This phase IIb study will evaluate the efficacy and the safety of 3 dose-levels of ABX464, administered daily in improving Modified Mayo Score (MMS) in patients with moderate to severe Ulcerative Colitis at Week 8.

Eligible patients will be randomized into 4 parallel intervention/treatment groups:

	Intervention/treatment Active Arm
Group #1: 25mg qd	1 capsule of 25mg ABX464 + 1 capsule of Placebo
Group #2: 50mg qd	1 capsule of 50mg ABX464 + 1 capsule of Placebo
Group #3: 100mg qd	2 capsules of 50mg ABX464
Group #4: Placebo	2 capsules of Placebo

The study design is presented below:



At Week 16, regardless of their clinical/symptomatic response and the actual treatment/dose received, patients willing to continue the study treatment and eligible for enrollment will roll over in an Open Label Extension study (ABX464-104). In this extension study, all patients will be dosed with ABX464 50mg QD. ABX464-104 is a separate clinical protocol subject to health authorities and ethics committee approvals.

In the present induction study (ABX464-103), randomization will be stratified according to the following factors:

1) US versus non-US patients
2) patients without previous exposure to biological or JAK inhibitors versus patients with previous exposure to biological drugs or JAK inhibitors.

The proportion of patients with previous exposure to biologics or JAK inhibitors will be limited to 60%, including a maximal proportion of patients with previous treatment with vedolizumab of 20%. The maximal proportion of patients with previous exposure with JAK inhibitors will be limited to 10%.

Patients will be treated for 16 Weeks in this induction study. All endoscopies (videos) will be centrally reviewed. E-Diaries will be used to collect frequency of stools, rectal bleedings, number of capsules taken and the intake time.

From Day 1 onwards, randomized patients will be seen at the investigational site on a regular basis (cf. flow-chart).

Flexible sigmoidoscopy with rectal and sigmoidal (if the sigmoidal is inflamed) biopsies will be performed at screening, at Day 57 +/- 4 days (week 8) and at Day 113 +/- 4 days (week 16). The Day 113 measurement will only be taken if patient does not experience endoscopic improvement at Day 57 (i.e.:

endoscopy sub-score of 2 or 3).

From Week 8 onwards, in the event of clinical progression of the disease defined as at least a 2-point increase from the screening in partial Modified Mayo Score (pMMS) with a Modified Mayo Score ≥ 4 confirmed by an endoscopy sub score of 2 points or higher, the patient will exit definitively the study.

Approximately 244 patients will be randomized in this study (i.e. 61 patients per study treatment arm).

3.1.2. Dose limiting toxicity (DLT)

A dose limiting toxicity (DLT) is defined as a grade 3 or higher adverse event as defined by the Common Terminology Criteria for Adverse Events (CTC-AE V5.0) considered by a safety review board as probably or definitely related to study treatment.

If more than 2 DLTs occur in the first five treated patients for at least 14 days, then the enrolment of additional patients in the concerned treatment group will be stopped, otherwise the enrolment of planned patients will be confirmed.

In addition, in case of a life threatening (grade 4) adverse reaction enrolment in the concerned treatment group and treatment of ongoing patients will be immediately discontinued.

In both cases, enrolment will only be resumed upon the decision of the sponsor if the Data Safety Monitoring Board can conclude that the causality of the event was unrelated or unlikely related to study treatment.

3.1.3. Data Safety Monitoring Board

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, to ensure the ethical conduct of the trial, to evaluate the 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 2 months.

The DSMB will oversee the adequate balance of baseline characteristics (gender, disease duration, concomitant treatment with corticosteroids, fecal calprotectin level, tobacco use) among the treatment groups.

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.

3.2. Duration of study participation

Eligible patients will be enrolled in the present study at the screening visit within 4 Weeks (28±3 days) prior to the first dosing, hence the maximum screening period is 31 days. However, patients can be randomized anytime within the screening window if all examinations are performed as per their schedule and results are available. Patients will be treated for 16 Weeks. At Week 16, regardless of their clinical/symptomatic response and the actual treatment/dose received, patients willing to continue the study treatment and eligible for enrollment will roll over in an Open Label Extension study (ABX464-104). In this extension study, all patients will be dosed with ABX464 50mg QD.

In any other cases, patients will exit the study (EoS visit to be performed within a Week after last dosing) and will be treated according to the standard of care.

Thus, the total duration of the study participation is 21 Weeks.

4. STUDY POPULATION

4.1. Number of Patients/Centers

Up to 244 patients will be randomized in this study. These patients will be enrolled in approximately 110 to 150 sites located in Europe, Canada and in the USA.

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:

- Men or women age 18 - 75 years;
- Diagnosis of moderate to severe active UC (including ulcerative proctitis if proximal extension of disease occurs beyond 10 cm) confirmed by endoscopy and histology at least 12 Weeks prior to screening visit. Moderate to severe active UC defined by Modified Mayo Score (MMS) of 5 to 9 inclusive (on a scale of 0-9). Moderate to severe active UC should be confirmed at screening visit with a centrally read endoscopy sub-score of at least 2 (on a scale of 0-3);
- Patients having either a documented inadequate response, no response, a loss of response, or an intolerance (defined as the occurrence of at least one Adverse Reaction leading to treatment discontinuation) to either immunosuppressant treatment (i.e., azathioprine, 6-mercaptopurine, methotrexate), tumor necrosis factor [TNF] inhibitors, vedolizumab, JAK inhibitors and/or corticosteroid treatment. Inadequate response, no response, loss of response is defined as:
  - Active disease or relapse in spite of thiopurines or methotrexate given at an appropriate dose for at least 3 months (i.e. azathioprine 2–2.5 mg/kg/day or mercaptopurine 1–1.5 mg/kg/day in the absence of leukopenia), and/or
  - Active disease despite corticosteroids treatment (prednisolone up to 0.75 mg/kg/day) over a period of 4 Weeks, and/or
  - Active disease or relapse in spite of adequate treatment (as defined in the SmPC) with tumor necrosis factor [TNF] inhibitors or vedolizumab, and/or
  - Active disease or relapse in spite of adequate treatment with JAK inhibitors over a period of at least 6 Weeks.
- Patients receiving oral corticosteroids must have been on a stable dose of prednisone or prednisone equivalent (≤20 mg/day) or on beclomethasone diproprionate (≤5mg/day) or on budesonide MMX (≤9 mg/day) for at least 2 Weeks prior to the screening visit;
- Topical corticosteroids and topical 5-aminosalicylic acid preparations must have been withdrawn at least 2 Weeks prior to the screening visit;
- Patients who are on oral 5-aminosalicylic acid must have been on a stable dose for at least 4 Weeks prior to the screening visit;
- Patients who are receiving immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate needed to be on a stable dose for at least 4 Weeks prior to screening visit. Patients taking methotrexate also are advised to take folic acid 1 mg/day (or equivalent) supplementation if there is no contraindication;
- Patients on probiotics (e.g., Culturelle® [Lactobacillus GG, i-Health, Inc.], Saccharomyces boulardii) must be on stable doses for at least 2 Weeks prior to the screening visit;
- Patients on antidiarrheals (e.g., loperamide, diphenoxylate with atropine) must be on stable doses for at least 2 Weeks prior to the screening visit;
- Patients who have received tumor necrosis factor [TNF] inhibitors, vedolizumab or other biologics must have discontinued therapy at least 8 Weeks prior to the screening visit due to lack or insufficient efficacy or intolerance;
- Patients previously treated with cyclosporine, tacrolimus or JAK inhibitors must have discontinued therapy at least 4 Weeks prior to the screening visit due to lack or insufficient efficacy or intolerance;
- Patients previously treated with tube feeding, defined formula diets, or parenteral alimentation/nutrition must have discontinued treatment 3 Weeks before the screening visit and

must be able to take, orally, appropriate amount of food (calories) and liquids to maintain body weight;

- Patients with surveillance colonoscopy defined as per ECCO guidelines;
- Patients with the following hematological and biochemical laboratory parameters obtained at screening:
    - Hemoglobin > 9.0 g dL^{-1};
    - Absolute neutrophil count ≥ 750 mm^{-3};
    - Platelets ≥ 100,000 mm^{-3};
    - Total serum creatinine ≤ 1.3 x ULN (upper limit of normal);
    - Creatinine clearance > 90 mL min^{-1} by the Cockcroft-Gault equation within 60 days prior to baseline;
    - Total serum bilirubin < 1.5 x ULN;
    - Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 2 x ULN;
- 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 at the screening visit 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 after end of study or early termination. Contraception should be in place at least 2 Weeks prior to study participation. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (WOCBP) will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception aiming at inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the patient. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with an infrequent or irregular menstrual cycle. Female and male patients must not be planning pregnancy during the trial and for 6 months post completion of their participation in the trial. In addition, male participants should use condoms and not donate sperm as long as contraception is required.

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 with Crohn's Disease (CD) or presence or history of fistula, indeterminate colitis (IC), infectious/ischemic colitis or microscopic colitis (lymphocytic and collagenous colitis);
- History of toxic megacolon, abdominal abscess, symptomatic colonic stricture or stoma; history or imminent colectomy, colonic malignancy;
- History or current evidence of colonic dysplasia or adenomatous colonic polyps. Patient with severe gastrointestinal complications; e.g., short bowel syndromes, recent or planned bowel surgery, Ileostomy and/or colostomy, recent bowel perforation;
- History of more than one episode of herpes zoster or a history (single episode) of disseminated zoster;
- Patients with active infections at screening such as infected abdominal abscess, Clostridium difficile (stool antigen and toxin required), CMV (positive IgM), TB and recent infectious hospitalization;
- Patients previously treated with ABX464;
- Acute, chronic or history of clinically relevant pulmonary, cardiovascular, hepatic, pancreatic or renal functional abnormality, encephalopathy, neuropathy or unstable CNS pathology such as seizure disorder, angina or cardiac arrhythmias, active malignancy or any other clinically significant

medical problems as determined by physical examination and/or laboratory screening tests and/or medical history;

- Acute, chronic or history of immunodeficiency or autoimmune disease;
- History of malignancy excluding patients considered cured (5 years disease free survivors);
- Serious illness requiring systemic treatment and/or hospitalization within 3 Weeks prior to baseline;
- Pregnant or breast-feeding women;
- Illicit drug or alcohol abuse or dependence;
- Patients who received live vaccine 30 days or fewer before first dose of study treatment and/or who's planning to receive such a vaccine during the study duration;
- Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer and during the study;
- Any condition, which in the opinion of the investigator, could compromise the patient's safety or adherence to the study protocol.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1. Study Flow Chart

Table displays hereafter a detailed study flow chart (with all assessments).

Table 1: Study Flowchart

		Study Treatment Period						
	D-28	D1	D8	D29	D57	D85	D113	EOS (within a week after last dose)
Time Window	± 3 days		± 2 days	± 2 days	± 4 days	± 4 days	± 4 days	± 2 days
Obtained Inform Consent	X							
Check of IN/EX Criteria	X	X						
Physical Examination	X	X	X	X	X	X	X	X
Body Weight (kg)	X	X	X	X	X	X	X	X
Height Measurement (cm)	X							
Medical History and Concomitant Medications	X							
Clostridium difficile (stool antigen and toxin), CMV, TB	X							
Vital signs	X	X	X	X	X	X	X	X
ECG (12 lead)	X	X			X		X	X
Randomization		X						
Blood Pregnancy test (WOCBP)	X	X		X	X	X	X	FU
Hematology + Biochemistry	X	X	X	X	X	X	X	X + FU
Coagulation and Troponin		X	X	X	X	X	X	
Serum collection for patients with loss of response to biologics (neutralizing antibody)		X						
Modified Mayo Score (pMMS/MMS)	X†	X	X	X	X	X	X	X
e-Diary data collection	X	X	X	X	X	X	X	
Fecal calprotectin		X			X		X	X
Sigmoidoscopy	X				X		X (Conditional)	
IBDQ		X			X		X	
ABX464/placebo treatment dispensation		X		X	X	X		
Blood samples drug pK		X*	X#	X#		X#	X*	
Blood sample Cytokines		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								

* Applicable to all randomized / D1: 0.5, 1.5, 3 h post-dose or 1, 2, 4 h post-dose; D113: pre-dose, 1, 2, 4 h post-dose or pre dose, 0.5, 1.5, 3 h post-dose. #: pre-dose only. FU = biological follow-up 3 Weeks after Day 120 (Hematology, Biochemistry and B-HCG) / No specific study visit required.
†: pMMS is calculated once within a week prior to screening endoscopy and Modified Mayo Score is calculated following endoscopy.

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.Screening Visit (Within 28 ± 3 days prior to Day 1)

The screening visit is within 4 Weeks (28 ± 3 days) prior to the first dosing, hence the maximum screening period is 31 days. However, patients can be randomized anytime within the screening window if all examinations are performed as per their schedule and results are available.

The patient will be informed about the general aspects of the study and will sign the screening informed consent form. The patient number will be allocated once the patient is screened in the IWRS. Only when consent has been given may further study procedures be carried out.

During the screening phase, the following assessments will be performed:

- Signed informed consent form;
- Demographic data: year of birth and gender;

- Disease extent (proctitis, left-sided or extensive), duration and disease activity, prior treatment and smoking status;
- Refractoriness to biologics (primary non-response or loss of response);
- Body weight and height;
- Medical history;
- Clostridium difficile (stool antigen and toxin), CMV (IgG and IgM), TB;
- Physical examination and vital signs;
- Hematology and Biochemistry including pregnancy test for all women of childbearing potential;
- 12 leads ECG;
- Sigmoidoscopy with rectal and sigmoidal (if the sigmoid is inflamed) biopsies (within 14 days prior to randomization/baseline); central read results must be available before randomization;
- Record endoscopy sub-score and transfer videos to central reader;
- Partial Modified Mayo Score (within a week prior to endoscopy) and Modified Mayo Score (once endoscopy is performed);
- Hand over the e-Diary to the patient and instruct the patient how to use it; e-Diary should be collected daily from screening to end of study;
- Record all medications received within 3 months prior to baseline and note if the medication is continuing;
- Record all UC medication without time limitation;
- Adverse Event reporting:
- Inclusion/exclusion criteria will be verified.

5.2.2.Baseline (First dosing day / Day 1)

- Randomization: The Investigator needs to check the inclusion/exclusion criteria (central read of the endoscopy and patient's symptom score from e-diary) with respect to the procedures performed at screening visit and if applicable proceed with the patient randomization. Treatment numbers will be allocated at randomization via the IWRS and dispensed to the patient;
- IBD Questionnaire (as the patient's first procedure);
- Physical examination and vital signs;
- Body weight;
- 12 leads ECG;
- Population Pharmacokinetics blood samples at either 0.5, 1.5, 3h (and 6 h and/or 10 h if possible) or at 1, 2, 4h (and 8 h and/or 12 h if possible);
- Hematology and Biochemistry including blood pregnancy test for all women of childbearing potential, coagulation parameters and troponin;
- Blood sample for miR-124 (PAXgene® tube) and cytokines determination;
- Serum collection for patients with loss of response to previous biologics (i.e. neutralizing antibodies);
- Fecal calprotectin dosage;
- Partial Modified Mayo Score;
- Review the patient e-Diary;
- Adverse Events reporting;
- Dispense study treatment to patient and instruct how to take them (First dosing at site);
- Schedule next patient visits.

5.2.3. Day 8, Day 29, Day 85 Visits

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry including coagulation parameters and troponin;

- Blood pregnancy test for all women of childbearing potential (D29 and D85 only);
- Blood sample for miR-124 (PAXgene® tube) and cytokines determination at Day 8 and Day 29 only;
- Check treatment compliance and review the patient e-Diary;
- Partial Modified Mayo Score;
- Population Pharmacokinetics blood samples pre-dose;
- Adverse Events reporting;
- Dispense study treatment (Day 29 and Day 85 only);
- Schedule next patient visits.

5.2.4. Day 57 and Day 113 Visits

- IBD Questionnaire (as the first visit procedure);
- Physical examination and vital signs;
- Body weight;
- At Day 113, population Pharmacokinetics blood samples at either pre-dose, 1, 2, 4h and if possible 48 h (Day 115 only) or pre-dose, 0.5, 1.5, 3h and if possible 48 (Day 115 only);
- Hematology and Biochemistry including blood pregnancy test for all women of childbearing potential, coagulation parameters and troponin;
- Blood sample for miR-124 dosage (PAXgene® tube) and cytokines determination;
- 12-leads ECG;
- Fecal calprotectin;
- Sigmoidoscopy with rectal/sigmoidal biopsies (Day 113 endoscopy is conditional on the response at Day 57);
- Modified Mayo Score at Day 57 (and Day 113 if available; OR pMMS at Day 113 if Day113 endoscopy not performed);
- Check treatment compliance;
- Adverse Events reporting;
- Study treatment dispensation at Day 57 visit;
- Review the patient e-Diary;
- At Day 113, enrolment of patients willing to take part to the maintenance phase;
- Schedule next patient visits.

5.2.5. End of Study Visit (Within a week after last dose ± 2 days)

This EoS visit applies to all premature discontinued patients and to patients not taking part to the maintenance study. Patients will perform an End of Study Visit (EoS) within a Week after last dosing (i.e D120 ± 2 days if the patient completed the study and is not taking part in maintenance study). Patients will be treated according to the standard of care from the last day of study treatment.

Following examinations/procedures should be performed:

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry and a follow-up 3 Weeks later;
- Partial Modified Mayo Score;
- 12 leads ECG;
- Fecal calprotectin;
- Adverse Events reporting.

NB#1: In case of premature discontinuation occurring during the treatment phase (D1-D113), the above examinations should be performed as an End of Study Visit 7 days ± 2 days after last dose.

NB#2: A biological follow-up, including hematology, biochemistry panel and a pregnancy test (if applicable), should be performed according to the central lab manual 3 Weeks after EOS (i.e Day 120 if the patient completed the study and is not taking part in maintenance study). In case of premature discontinuation, this biological follow up should be performed 3 weeks after the last dose. No specific study visit is required. Potential Adverse Event or Clinically significant abnormal value should be reported according to the section 8.4 of the study protocol.

5.3. Detail of the study assessments

5.3.1.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.

5.3.2. Adverse Events of Interest

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

- In case of occurrence of a skin lesion (regardless of its severity), a dermatologist consultation should be scheduled to evaluate the type of lesion, its severity and etiology. An anonymized medical report shall be provided to the Sponsor.
- In case of occurrence of a headache episode lasting more than a week and refractory to standard painkillers (Ibuprofen, acetaminophen, paracetamol, etc.…), a specific questionnaire will be filled in by the patients to better characterize the attributes of the event (Appendix #4).

5.3.3. Pregnancy

For all female patients of childbearing potential, a blood pregnancy test (beta human chorionic gonadotropin [HCG]) will be performed at Day -28, Day 1, Day 29, Day 57, Day 85 and Day 113. In case of positive pregnancy testing, detailed procedures can be found in section 8.4.2.

5.3.4. ECG

Electrocardiograms will be performed at Day -28, Day 1, Day 57, Day 113 and EoS visit. 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 with the patient in a resting position. Prior to the recording the patient should be at rest for at least five minutes. Resting ECG is recommended to 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 -28 must be documented as adverse events.

5.3.5. IBD Questionnaire (IBDQ)

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a widely used questionnaire for HRQoL 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 Day 1, Day 57 and Day 113 prior to any study procedures.

5.3.6. 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.

Total Mayo score consists of 4 items: stool frequency, rectal bleeding, flexible sigmoidoscopic examination, and a physician global assessment (Appendix #3). Modified Mayo Score (MMS) consists of 3 items (stool frequency, rectal bleeding, flexible sigmoidoscopic examination).

Partial Modified Mayo Score (pMMS) consists of only 2 items (stool frequency, rectal bleeding).

Although the physician global assessment is performed as part of the patient care, only the pMMS and MMS will be assessed as endpoints according to regulatory guidance. Stool frequency and rectal bleeding frequency will be recorded from the patient e-Diary at each patient visit by the Investigator.

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

5.3.7. Sigmoidoscopy with rectal/sigmoidal biopsies

Sigmoidoscopies procedures (or colonoscopies if applicable) 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 who are blinded to the treatment and visit sequence of the recordings.

The central reader's score at Screening, Day 57 and Day 113 (if available) will be entered directly into the eCRF. Screening videos will be evaluated for eligibility and scores communicated to sites within four (4) business days. 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 Screening, at Day 57 and at Day 113 (if applicable). The two (or 4) biopsies 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.

5.3.8. Hematology and biochemistry

For hematology and biochemistry central laboratory will be used (i.e. Eurofins). All lab dosages will be done centrally. Sampling kits and transportation information and devices will be provided by Eurofins. Due to the outbreak of the SARS Cov-2 pandemic, some patients may not attend the study site, therefore hematology and biochemistry measurements may be done locally to assess the safety.

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

The results of fecal calprotectin levels will not be communicated to either the study Sponsor or the Investigational site during the study in order to avoid any possible bias related to disease evaluation.

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

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

Table displays the clinical laboratory parameters that must be measured.

Table 2: Laboratory Tests

HEMATOLOGY	BIOCHEMISTRY	STOOLS
Hemoglobin	Sodium	Fecal calprotectin
Hematocrit	Potassium	
WBC	Chloride	
Neutrophils	Calcium	
Lymphocytes	Phosphate	
Monocytes	Glucose	
Eosinophils	BUN or urea	
Basophils	Creatinine	
Platelet count	AST	
Prothrombin time (From D1 to D113 only)	ALT	
Fibrinogen (From D1 to D113 only)	GLDH	
	Lipase	
	Alkaline phosphatase	
	gGT	
	Total bilirubin	
	Total protein	
	Albumin	
	LDH	
	CRP	
	Total cholesterol	
	HDL cholesterol	
	LDL cholesterol	
	Troponin I & T (From D1 to D113 only)	

At each biochemistry time point, a tube containing the remaining serum (at least 1 mL) should be kept and stored at -20°C for potential further liver function parameters such as soluble caspase-cleaved keratin 18 (M30 Elisa) and/or miRNA22 as a marker of early hepatotoxicity.

5.3.9. Cytokines analysis

Cytokines (IL-6, TNFα, IL-1b, IL-10, MCP-1 but not limited to) will be assessed by the central laboratory. The process for samples preparation, storage and shipment will be fully defined in the laboratory manual.

5.3.10. 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.

5.3.11. Pharmacokinetics

Blood samples will be collected in all patients for PK assessment. Sampling will be performed on Day 1 and on the last day of study treatment. Two elementary sampling designs will be used to limit the number of samples in each patient:

- Group 1:
  - Day 1: 0.5, 1.5, 3 (and 6 h and/or 10 h if possible)

  - Last day (Day 113): predose, 1, 2, 4 and if possible 48 h (Day 115). D115 will only be taken if the subject is not transitioning to the ABX464-104 study.
- Group 2:
  - Day 1: 1, 2, 4 (and 8 h and/or 12 h if possible)
  - Last day (Day 113): predose, 0.5, 1.5, 3 and if possible 48 h (Day 115). D115 will only be taken if the subject is not transitioning to the ABX464-104 study.

In addition to these sampling time points, pre-dose concentrations could be collected at the study visit day 8, 29, 85. Patient data will be pooled with data obtained in previous clinical studies in order to build a population pharmacokinetic models for ABX464 and its metabolite.

5.4. Summary of blood samples

The Table below summarizes the volume of blood to be sampled at each study visit.

Table 3: Blood Volume

	COLLECTION TUBE	SCR D-28	BSL D1	D8	D29	D57	D85	D113	EOS D120	FU	TOTAL
Hematology (Hemoglobin, Hematocrit, Red Cell Count, MCV, MCHC, Platelets, White cell count with diff.)	EDTA tube	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	**18.0**
Biochemistry panel incl CRP, GLDH, Serum Pregn and lipids	Serum gel tube	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	**76.5**
Fibrinogen and Prothrombin Time	Na-citrate tube		4.5	4.5	4.5	4.5	4.5	4.5			**27.0**
Troponin (I&T)	SST tube with gel		3.5	3.5	3.5	3.5	3.5	3.5			**21.0**
CMV IgG and IgM	Serum gel tube	3.5									**3.5**
Neutralizing antibodies (biologics)	Serum 2 mL gel tube		2.0								**2.0**
Quantiferon TB Gold Plus	4x 1mL tube	4.0									**4.0**
Cytokines (IL-6, TNFa, IL-1b, IL-10)	Serum gel tube		8.5	8.5	8.5	8.5	8.5	8.5			**51.0**
PAXgene Tube (miRNA)	PAXgene		5.0	5.0	5.0	5.0	5.0	5.0			**30.0**
PK samples	Serum tube		10.0	2	2			10.0			**24.0**
	Total per visit	**18.0**	**44.0**	**34.0**	**34.0**	**32.0**	**32.0**	**42.0**	**10.5**	**10.5**	**257.0**

6. INVESTIGATIONAL MEDICINAL PRODUCT(S)

All investigational medicinal 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 IIb study consists of capsules containing ABX464 or its matching placebo given orally once daily for 113 days.

6.2. Description of investigational medicinal product

6.2.1. Active investigational medicinal product (ABX464)

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

For the proposed clinical trial, the IMP consists of size 01 capsules containing either 25mg or 50mg of ABX464 drug substance in the form of granulate prepared with a number of common excipients [redacted] It is supplied in study specific child-resistant blister cards.

ABX464 will be manufactured by:

[redacted]

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

[redacted]

6.2.2. Placebo

The matching placebo consists of the same hard gelatin, powder-filled capsules (size 01) filled with only the same common excipients [redacted] as the active IMP. It is supplied in study specific child resistant blister cards.

ABX464 matching placebo will be manufactured by:

[redacted]

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

[redacted]

6.3. Administration and Dosing

6.3.1. Administration of the investigational medicinal product

Depending on the randomization, patients will be treated with a daily dose of either 25mg, 50mg or 100mg of ABX464 or matching placebo. All patients regardless of the treatment group will receive 2 capsules every day.

Patients will be orally dosed in a fed condition (regular meal) in the morning with a glass of water.

An e-Diary, in which the patient should report the number of capsules taken and the intake time from baseline visit onwards, will be given to the patient at screening.

6.3.2. Guidelines for treatment postponement and dose modifications

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

6.4. Method of Assigning Patients to Treatment Arms

All patients will be assigned a unique and incremental Patient Identification (ID) number. Patient IDs will be unique (i.e. reallocation of the ID will not be permitted). The format will be a seven-digit number as follows: ABX-country/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 non-US patients (i.e. those who fulfil all inclusion/exclusion criteria) will be randomized according to a 1:1:1:1 ratio to ABX464 100mg: ABX464 50mg: ABX464 25mg: placebo treatment arms.

Randomization will be performed via IWRS. Treatment numbers will be allocated first at randomization and then every month (i.e. D29, D57 and D85).

In all cases, patient should return his/her used and unused blister cards at each study visit for a compliance check.

6.5. Blinding and breaking the study blind

Study drug will be packaged in blinded label child resistant blister cards. Blister cards will be numbered according to a randomized treatment number list. The content of the labeling is in accordance with the required references listed in the Good Manufacturing Practices.

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

Investigators may have access to unblinding at any time via the pharmacovigilance hotline.

6.6. Packaging

The IMP consists in hard gelatin, powder-filled capsules (size 01) containing 25 or 50 mg of ABX464 supplied in study specific child-resistant blister cards.

6.7. Storage

ABX464/Placebo capsules will be shipped to the investigational site at a temperature not above [redacted]

[redacted]

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

6.8. Product Accountability

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

6.9. Prior and Concomitant Medication

6.9.1. Allowed concomitant treatment

Allowed Concomitant Medications are:

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

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, duration, indication and the time of last intake before all PK samplings.

6.9.2. Prohibited concurrent medications

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

- Tumor necrosis factor [TNF] inhibitors, vedolizumab or others biologic therapies with a wash-out period of at least 8 Weeks prior to the screening visit;
- JAK inhibitors with a wash-out period of at least 4 Weeks prior to the screening visit;
- Topical corticosteroids and topical 5-aminosalicylic acid preparations with a wash-out period of at least 2 Weeks prior to the screening visit;
- Cyclosporine and tacrolimus with a wash-out period of at least 4 Weeks prior to the screening visit;
- Vaccination with live components during the study and up to 8 Weeks after the last dosing;
- Drugs that could interact with ABX464 should be avoided especially the CYP1A2 substrates (cf. Appendix #1). The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (Clozapine, theophylline, ropinirol, warfarin and methadone). In case of concomitant treatment with ondansetron the maximal daily dose must be limited to 8 mg;
- Drugs that inhibit or induce CYP1A2 (cf. Appendix #1).
- Drugs that inhibit UGTIA9 activity and inhibitors of OATP1B1/1B3 transporters (cf. Appendix #1).
- Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer and during the study.

7. PATIENT COMPLETION AND WITHDRAWAL

7.1. Patient Completion

Treatment with ABX464/Placebo shall continue until Day 113, except if a patient fulfils a premature discontinuation criterion (defined below). After Day 113, patients who are willing to carry on the study treatment will be able to take part in the long-term maintenance study (ABX464-104).

In any other case, patients will exit the study (EoS) and will be treated according to the standard of care. The ABX464-104 follow-up study is a separate clinical protocol subject to health authorities and ethics committee approvals.

7.2. Premature trial discontinuation

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

- Investigator's decision; patient that 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 off from study treatment;
- 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%).
- Worsening of the UC defined, from Week 8 onwards, 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;
- Major protocol violation;
- Patient's decision;
- Withdrawal of consent;

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

7.3. Study Discontinuation

All patients (Except those transitioning to the ABX464-104 study), regardless of the completion or premature discontinuation, should perform the End of Study Visit according to the study flow-chart,.

7.4. Screen and Baseline Failures

A patient is considered to be a baseline failure if the patient signs the informed consent but withdraws before the baseline visit. All potential patients who are screened for enrolment in this study will be listed on the patient Screening Log/Identification List. Reasons for exclusion will be recorded for potential patients who do not enter the study.

A patient who does not fulfil the randomization criteria will be considered as a screen failure. All patient data should be entered in the eCRF including the screen failure data.

Based on the investigator evaluation and sponsor prior approval, a non-randomized patient can be re-screened. This re-screening procedure should be documented, the patient should consent again and a new unique and incremental patient Identification (ID) number be allocated.

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

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

During the screening period, all adverse events will be collected.

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

8.1. Definitions

8.1.1. Definition of an AE

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

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

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

8.1.2. Adverse Drug Reactions (ADR)

A response to a medicinal product which is noxious and unintended. Suggesting that there is at least a reasonable possibility or suspicion of a causal relationship between the medicinal product and an adverse event.

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

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

a) Results in death

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

b) Is life-threatening

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

c) Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization means that the patient has been detained 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.

8.2. A Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

8.3. Events and/or Outcomes Not Qualifying as SAEs

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

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

8.4. Events or Outcomes Qualifying as AEs or SAEs

8.4.1.Clinical laboratory parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g. vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definitions of sections 8.1.1.. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at informed consent and significantly worsen during the study will be reported as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied and are present at the start of the study 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.

8.4.2.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 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.

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

The time period for collecting pregnancy information is identical to the time period for collecting AEs, as stated in Section 8.5, Time Period, Frequency, and Method of Detecting AEs and SAEs. Pregnancy information is collected from the signing of informed consent to 4 Weeks after the last dose.

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

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

Moreover, any occurrence of pregnancy within 3 months post stopping dosing must be reported.

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

IntuVigilance Limited

Scotsbridge House, Scots Hill
Rickmansworth WD3 3BB
Hertfordshire, UK
Hotline phone: [redacted]

Email Address: [redacted]

Fax number: [redacted]

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

8.6. Recording AEs and SAEs

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

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

The following points must be recorded for each event:

- A description of the event in medical terms, not as reported by the patient;
- Date of onset (start date);
- Date of resolution (stop date);
- The time of onset with respect to administering the investigational medicinal product;
- The severity of the sign/symptom or clinically significant abnormal laboratory value according to CTC-AE Classification (Version 5.0);
- The causal relationship between the investigational medicinal 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 medicinal 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 medicinal product? And answered "NO" (if not related) and "YES" (if related);
- Action taken regarding the investigational medicinal product:
  - No action;
  - Temporary discontinuation;
  - Permanent discontinuation;

- Recovered without sequelae / resolved without sequelae;
- Recovered with sequelae / resolved with sequelae;
- Recovering/Resolving;
- On-going;
- Fatal (for SAEs only).

- Patient's outcome.

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

8.7. Reporting of SAEs to ABIVAX or its designee

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

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

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

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

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

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

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

8.8. Reporting of SAEs to Regulatory Authorities

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

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

Safety reports on adverse events that are serious AND unexpected AND causally associated with the investigational medicinal 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

No interim analysis is planned.

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

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

9.1.2. Definition of study analysis sets

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

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

9.1.3. Patients/Patients disposition

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

9.1.4. Demographic and other baseline characteristics

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

9.1.5. Treatment compliance

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

9.2. Efficacy Analysis

Analysis of efficacy data will be carried out in the Full Analysis Set in which subjects who prematurely discontinue the study due to adverse reaction(s) will be considered treatment failures.

The primary efficacy endpoint of the study is the change in the Modified Mayo Score (MMS) from Baseline to Week 8. This change will be compared between subjects who received ABX464 and placebo for each ABX464 treatment arm separately using an ANCOVA model adjusting for randomized study treatment arm, previous biological or JAK inhibitors treatment use (i.e. randomization strata), and baseline MMS.

The dose testing will commence with comparing the ABX464 50mg dose with placebo. If this is significant at a 5% two-sided level (i.e. $p<0.05$) a comparison against placebo will be carried out at the ABX464 100mg dose. Again, if significance at a 5% level for this test is observed the procedure will be repeated at the ABX464 25mg dose. In this closed procedure no adjustment for multiple comparison is needed. Should the data warrant it, testing between doses may also be conducted.

In addition, descriptive statistics will be presented by treatment arm for all secondary efficacy variables for each measurement timepoint.

These statistics include:

- Continuous variables: mean, standard deviation, minimum and maximum, 95%
- Confidence intervals for the mean, median and quartiles will be presented.
- Categorical variables: counts, rates and 95% confidence intervals for the rates will be calculated.

In addition to descriptive statistics, the following analyses will also be carried out for the variables indicated below:

- The global (combined) ABX464 treatment effect vs. placebo in the change from Baseline in Modified Mayo Score at Week 8
- The proportion of subjects with clinical remission at Week 8 will be compared across study treatment arms using a stratified Mantel-Haenszel test.
- Mixed model analysis of covariance will be conducted for the following measurements:
    - The change from baseline in microRNA-124 levels in total blood (PAXgene®) at Week 1, Week 4, Week 8 and Week 16 and in tissue (RNA later).
    - The change from baseline in fecal calprotectin levels at Week 8 and Week 16.
    - The change from screening in the histopathology/infiltrate (rectal/sigmoidal biopsies) assessed by the Robarts Histopathology Index, the Geboes and Nancy Histology Scoring Scales at Week 8 and Week 16 (if available).
    - The change from screening in Modified Mayo scores and Partial Mayo scores during the study.

In this mixed model, treatments and stratum will be fixed effects, subject will be random effect and baseline values of the respective measurements will be covariates. Other explanatory variables will also be allowed to be included in the model. To normalize eventual skewed distributions transformation of the data will also be considered. Study treatment groups will be compared within this model framework. All p-values will be interpreted in a descriptive manner.

The following subgroups will be analyzed:

- Gender
- Age
- Country
- US vs non-US
- Baseline MMS
- With/without previous biological or JAK inhibitors treatment
- Week 16 ABX464-NGlu AUC0-12 level above/below 7 000 h*ng/mL (vs. placebo)
- Concomitant UC medications.

9.2.1. Pharmacokinetics

Population PK data analysis will be performed via three steps:

- Data preparation and exploratory: The analysis dataset will be created and formatted according to MONOLIX or NONMEM requirement using SAS®. An exploratory analysis by visual inspection

of PK profiles/dose normalized PK profiles in natural and semi-log scale will be performed in order to anticipate the type of PK model (number of compartments, linear or saturable elimination, etc)

- Population PK model development: A PopPK model consists of four basic components:
  - The structural PK model, which defines the PK parameters and describes the plasma concentration-time profiles of ABX464 and its metabolite.
  - The inter-individual variability model component, which describes the inter-individual variability of PK parameters in the population
  - The residual error model component, which describes the underlying distribution of the error in the measured concentrations.
  - The covariate model component, which describes the influence of covariates such as demographic data on PK parameters.

  The search for the final model will follow the following strategy:
  - Selection of the simplest structural model, which predicts the plasma concentration as a function of time and dose, based on smallest objective function and by the pattern in the residual plots. The best estimation method, the most appropriate inter-individual variability (IIV) models, and the residual error model, are identified. The resulting model is called BASE model.
  - Test of influence of selected covariates.
  - Refinement of inter-individual variability model and residual error models
- Model validation: Goodness of fit plots will be assessed for each important step of model building. For the final model, a visual predictive check (an evaluation graph based on simulation) will be provided.

Data will be prepared using SAS version 9.2. Population analysis will be performed using MONOLIX version 2018 R1 or NONMEM version 7.2. Graphs will be provided using SAS.

9.3. Safety Analyses

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

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

Two periods will be defined for TEAE:

- Any adverse event which occurs or worsens from first dosing to Day 113;
- Any adverse event which occurs after Day 113.

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

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

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

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

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

9.3.1. Clinical laboratory evaluation

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

In addition, shift tables from baseline will be presented.

9.4. Determination of Sample Size

The primary endpoint is the change in the Modified Mayo Score (MMS) from Baseline to Week 8. The primary endpoint will be compared between subjects who received ABX464 and placebo for each ABX464 treatment arm separately.

For the sample size calculation, the following assumptions were made:

- mean reduction in MMS (ABX464): 2.5
- mean reduction in MMS (placebo): 1.0
- pooled standard deviation of reduction in MMS: 2.1
- Type 1 error: 5% two-sided.
- Treatment testing to use a sequential, gate-keeping strategy, where treatment arms will be tested in the following order: ABX464 50mg vs. placebo, ABX464 100mg vs. placebo, ABX464 25mg vs. placebo. Subsequent tests will only be performed only if prior test(s) are significant ($p<0.05$).
- >90% power
- Two-sample t-test
- 5% dropout rate prior to Week 8 MMS assessment (all treatment arms)
- 1:1:1:1 (ABX464 100mg: ABX464 50mg: ABX464 25mg: placebo) study treatment arm allocation ratio.

If the above assumptions hold true, then a total sample size of 232 subjects will be required to be randomized (58 subjects randomized to each study treatment arm).

Due to the SARS Cov-2 pandemic the drop-out rate of the study is expected to be somewhat higher than originally estimated. Therefore, an additional 12 subjects are planned to be recruited in the study leading to an overall sample size of 244 patients (61 subjects randomized to each study treatment arm).

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 medicinal products.

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

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

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

10.1.2. Independent Ethics Committee/Institutional Review Board

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

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

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

10.1.3. Patient Informed Consent

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

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

The patient must be 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 a "*Investigator site staff signature and task delegation log*" form, showing the signatures and initials of any person who is authorized to make or change entries in the eCRF and any person authorized to electronically sign the eCRF.

The eCRF used for this study is validated and fulfils the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) requirements, European and FDA (21 CFR Part 11) regulations.

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

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

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

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

11.2. Data management

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

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

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

11.3. Data coding

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

11.4. Randomization

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

11.5. Study Monitoring

The study will be conducted in accordance with the ICH Note for Guidance on GCP (ICH, Topic 6, 1996). The appointed monitor will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ABIVAX requirements. Throughout the study, the monitor will arrange visits to the study center at appropriate intervals to assess the progress of the study and review the completed eCRFs.

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 medicinal product;
- Verify that the site staff and facilities continue to be adequate for the proper conduct of the study;
- Ensure that the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements;
- Help resolve any problems that may have arisen.

In line with ICH GCP guidelines, monitoring will include verification of data entered in the CRF against the original 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.

11.6. Records Retention

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

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

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

11.7. Quality Assurance and Inspection by Authorities

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

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

- Record retention.

11.8. Study and Site Closure

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

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

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

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

11.9. Study report and Publication

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

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

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

11.10. Ownership and Confidentiality

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

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

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12. APPENDICES

Appendix 1:

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

Substrates: **Alosetron, Duloxetine, Ramelteon, Tasimelteon,** Amitriptyline, Clomipramine, Imipramine, Agomelatine, **Clozapine**, Olanzapine, Haloperidol, Ropivacaine, **Theophylline,** Zolmitriptan, Tamoxifen, Erlotinib, Cyclobenzaprine, Mexiletine, Naproxen, Ondansetron, Phenacetin, Paracetamol, Propranolol, Tacrine, **Tizanidine**, Verapamil, **Warfarin**, Zileuton, **Ropinirole, Methadone.** Inhibitors: Artemisinin, Atazanavir, **Ciprofloxacin, Enoxacin**, Ethinyl Estradiol, **Fluvoxamine,** Mexiletine, Tacrine, Thiabendazole, Zileuton Inducers: **Montelukast, Phenytoin, Rifampin, Ritonavir, Teriflunomide**

OATB1B1/1B3 inhibitors (prohibited concomitant medications)

Inhibitors: **Cyclosporine, Eltrombopag, Lapatinib, Lopinavir, Rifampin, 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 w 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 chose 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 needir 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 enga(
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 fi
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 c 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 gettin 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 choo 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 bleedi 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 retching 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: Headache Questionnaire

Follow Up Headache Questionnaire

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

Please describe your headaches:

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

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

2. How frequent are your headaches?

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

3. How long do your headaches last in days?

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

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

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

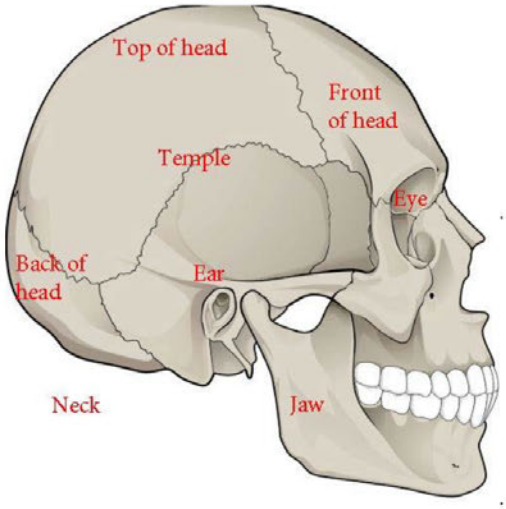
**If YES to above, please focus the following questions on your worst disability headache type*

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. 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		

11. 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: _____	