Title: A Phase IIa study to evaluate the safety and efficacy of ABX464 50 mg once daily versus Placebo in Subjects with Moderate to Severe Active Ulcerative Colitis who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab and/or corticosteroids

NTC Number: NCT03093259

Protocol approve date : March 13, 2018

CLINICAL STUDY PROTOCOL
ABX464-101

Sponsor:	ABIVAX 5, rue de la Baume 75008 Paris FRANCE
Investigational product:	Not Available
Product code:	ABX464
Therapeutic indication:	A Phase IIa study to evaluate the safety and efficacy of ABX464 50 mg once daily versus Placebo in subjects with Moderate to Severe Active Ulcerative Colitis who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab and/or corticosteroids
EudraCT number:	2017-000937-30
Study code:	ABX464-101
Version number:	2.0
Release date:	March 13, 2018

CLINICAL STUDY PROTOCOL

Study code	ABX464-101
Investigational product code	ABX464
EudraCT number	2017-000937-30
Detailed Title	A Phase IIa study to evaluate the safety and efficacy of ABX464 50 mg once daily versus Placebo in subjects with Moderate to Severe Active Ulcerative Colitis who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab and/or corticosteroids.
Study Phase	Phase IIa
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INVESTIGATOR AGREEMENT PAGE

EudraCT number 2017-000937-30

Detailed Title: A Phase IIa study to evaluate the safety and efficacy of ABX464 50 mg once daily versus Placebo in subjects with Moderate to Severe Active Ulcerative Colitis who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab and/or corticosteroids.

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

- To conduct the study as outlined in the protocol, any mutually agreed future protocol amendments and with all the terms and conditions set out by ABIVAX.
- Not to implement any changes in the procedures described in the protocol without the prior approval of the sponsor and prior to review and written approval by the Ethics Committee and/or Regulatory Authorities, unless instructed otherwise by the Regulatory Authorities or the wellbeing of subjects is jeopardized.
- To conduct the study in accordance with the ICH GCP 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 2001/20/EC, the provisions of the Helsinki Declaration, and relevant legislation in force.
- I am thoroughly aware of the study drug specifications and adverse events as described in the protocol and the current Investigator's Brochure and any other information provided by the Sponsor.
- To ensure that sub-investigator(s) and other relevant members of my staff involved in the study are fully aware of their responsibilities regarding this study and will conduct the study according to the protocol.

Investigator's Name: _____

Investigator's Signature: _____

Date: _____

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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
AUC_{0-24}	area under the plasma concentration-versus-time curve from zero to 24 hours
$AUC_{0-\infty}$	area under the plasma concentration-versus-time curve from zero to infinity
AUC_{0-t}	area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration
AUC_{0-t}	area under the plasma concentration-versus-time curve from time zero to the dosing interval
BMI	body mass index
CI	confidence interval
C_{max}	peak plasma concentration
CRF	case report form
CTC-AE	Common Terminology Criteria for Adverse Events, version 4.0
CTFG	Clinical Trial Facilitation Group
DBP	Diastolic Blood Pressure
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
F_{rel}	relative bioavailability
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
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-22	Interleukine 22
IMP	Investigational Medicinal Product
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
o.d.	Once Daily
PCSA	potentially clinically significant abnormalities
PD	pharmacodynamics
PK	pharmacokinetics
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
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SF-36	Quality of Life Questionnaire
SOC	system organ class
$t_{1/2}$	terminal half-life
TEAE	treatment emergent adverse event
t_{lag}	interval between administration time and the sampling time preceding the first concentration above the limit of quantification
t_{max}	time to peak plasma concentration
UC	Ulcerative Colitis
Vd/F	volume of distribution
vs.	versus

1. INTRODUCTION AND STUDY RATIONALE

1.1. Ulcerative Colitis (UC)

1.1.1. Disease

[redacted]

1.1.2. Management of subjects

[redacted]

1.2. ABX464 rationale

1.2.1. Investigational treatment description

[redacted]

[redacted]

1.2.2. Investigational product description

[redacted]

[redacted]

1.2.3. Investigational product Mode of Action

[redacted]

1.2.4. Rationale for the development of ABX464 in Ulcerative Colitis

[redacted]

[redacted]

[redacted]

1.2.5. Preclinical data of ABX464

1.2.5.1. Non-clinical background information

[redacted]

[redacted]

1.2.6. Previous clinical experience with ABX464

[redacted]

1.3. Rationale for the clinical study and study design

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of the study is to evaluate the safety of ABX464 given at 50 mg once daily versus Placebo in subjects with Moderate to Severe Active Ulcerative Colitis who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab and/or corticosteroids.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the effect of ABX464 on the expression of IL-22 in serum and rectal/sigmoidal tissue compared to placebo in Subjects with Moderate to Severe Active Ulcerative Colitis.
- To evaluate the effect of ABX464 on miR-124 expression in whole blood (PAXgene®) and in tissue (RNA later) vs placebo in Subjects with Moderate to Severe Active Ulcerative Colitis.
- To evaluate the effect of ABX464 on the rectal/sigmoidal infiltrates (Geboes score) vs placebo in Subjects with Moderate to Severe Active Ulcerative Colitis.
- To evaluate the effect of ABX464 on the rectal microbiome compared to placebo in subjects with Moderate to Severe Active Ulcerative Colitis
- To evaluate the effect of ABX464 on endoscopic remission vs placebo in Subjects with Moderate to Severe Active Ulcerative Colitis.
- To evaluate the effect of ABX464 on clinical remission and response vs placebo in subjects with Moderate to Severe Active Ulcerative Colitis.
- To evaluate the effect of ABX464 on Quality of Life (QoL) measured by the SF-36 questionnaire vs placebo in Subjects with Moderate to Severe Active Ulcerative Colitis.
- To assess the Pharmacokinetics parameters of ABX464 in Subjects with Moderate to Severe Active Ulcerative Colitis.

2.3. Primary Endpoint

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

2.4. Secondary Endpoints

The secondary endpoints of this study are:

Primary efficacy endpoint:

- The proportion of subjects receiving ABX464 with clinical remission according to the Total Mayo Score at week 8 compared to placebo. Remission exclude friability and is based on total Mayo score ≤ 2 with no individual sub-score > 1.

Other secondary endpoints:

- The change from screening in IL-22 expression levels in serum and rectal/sigmoidal tissue at week 8 compared to placebo.
- The change from baseline in microRNA-124 levels in whole blood (PAXgene®) and in tissue (RNA later) at week 4 and week 8 compared to placebo.
- The change from baseline in fecal calprotectin levels at week 4 and week 8 compared to placebo.
- The change from screening in the histopathology/infiltrate (rectal/sigmoidal biopsies) assessed by the

Geboes score at week 8 compared to placebo.

- The change from screening in rectal microbiota using taxonomic markers at week 8 compared to placebo.
- The change from screening in Total Mayo Score in subjects receiving ABX464 at week 8 compared to placebo.
- The change from baseline in Partial Mayo Score in subjects receiving ABX464 at week 4 and week 8 compared to placebo.
- The proportion of subjects achieving endoscopic remission at week 8. Endoscopic remission is defined as a Mayo endoscopic sub-score of 0.
- The proportion of subjects achieving improvement in endoscopic appearance at week 8. Improvement of endoscopic appearance is defined as a Mayo endoscopic sub-score of ≤ 1.
- The proportion of subjects achieving a symptomatic remission at week 8. Symptomatic remission is defined as a total Mayo Score ≤ 2 with no individual sub-score > 1 and rectal bleeding and stool frequency sub-scores of 0.
- The time to UC worsening after week 8.
- The serum concentration evaluation of ABX464 and its metabolites levels.
- The scores and changes from baseline in SF-36 Questionnaire scores at week 4 and week 8.
- The number of incidences of treatment-emergent serious adverse events.
- The number of incidences of treatment-emergent adverse events of special interest.
- The number of incidences of adverse events leading to investigational product discontinuation.
- The number of incidences of specific laboratory abnormalities.

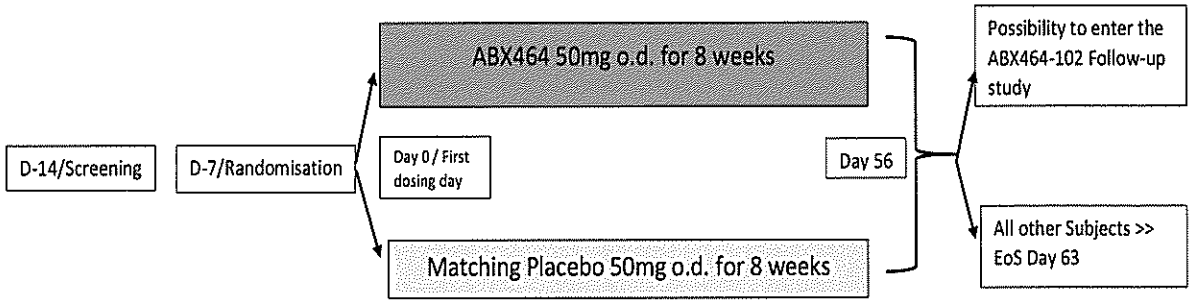
3. INVESTIGATIONAL PLAN

3.1. Study design

3.1.1. Design and methodology

This Phase IIa study is an 8-week, double-blind, placebo-controlled, randomized study aimed at evaluating the safety and the efficacy of ABX464 given once a day (*o.d*) at 50 mg in subjects with moderate to severe Active Ulcerative Colitis who have failed or are intolerant to immunomodulators, Anti-TNFα, vedolizumab and/or corticosteroids followed by a one-month follow-up period.

Eligible subjects will be randomized according to a 2/1 ratio in two different groups of treatments according to the following study design.



Upon screening visit (D-14), eligible subjects will be checked for eligibility.

Subject eligibility will be confirmed by the medical staff based of the endoscopy central reading and on the laboratory results performed at screening visit. If eligibility is confirmed, then the subject will be randomized using the eCRF.

At Day 0, study drug (ABX464 or its matching placebo) will be added on top of this background therapy for the next 56 days. ABX464 or its matching placebo will be given once a day at 50 mg.

For subjects receiving oral corticosteroids during the study treatment period, tapering of steroids should start at week 4 at a rate of prednisone or prednisone equivalent 5 mg/week for 4 weeks to discontinuation. However, this study procedure is left to the Investigator's discretion.

The dose of 50 mg of the study drug has been selected based on the reassuring safety data accumulated on the 50 mg o.d. from previous studies and the high exposure in ABX464-NGluc (active metabolite) at this dose.

Eligible subjects will be randomized according to a 2/1 ratio in two different groups of treatments.

Randomization will be stratified according to the following factors: concomitant treatment with corticosteroids and previous TNF antagonist exposure.

Randomized subjects will be seen at the investigational site every week during the first month of treatment and then every two weeks during the second month. Flexible sigmoidoscopy with rectal and/or sigmoidal biopsies will be performed again at week 8.

The DSMB will meet after every 3 subjects are recruited in order to review on a regular basis the safety profile of this dose level and to recommend, if appropriate, the continuation of the study.

The sample size in this Proof of Concept study is 20 subjects receiving ABX464 and 10 subjects receiving Placebo (i.e. a total of 30 subjects).

3.1.2. Tapering period

For subjects receiving oral corticosteroids during the study treatment period, a tapering of steroids should start at week 4 at a rate of prednisone or prednisone equivalent 5 mg/week for 4 weeks. However, this study procedure is left to the Investigator's discretion.

3.1.3. 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 v4.0) considered by a safety review board as probably or definitely related to study treatment. The first three subjects will be enrolled first and followed up for at least 2 weeks of treatment. If more than one DLT occur of the first three treated subjects, then the enrolment of additional subjects will be stopped, otherwise the enrolment of planned subjects will be confirmed.

In addition, in case of a life threatening (grade 4) adverse reaction enrolment and treatment of ongoing subjects 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.

3.1.4. 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 subjects, insure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.

The DSMB will meet first after the 3 first subjects are enrolled and treated for at least 2 weeks and then every group of 3 subjects. Besides, the DSMB may recommend the early termination of the trial at any time if an unacceptable toxicity occurs.

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 subjects will be enrolled in the present study at the screening visit 2 weeks prior to the first dosing. Subjects will be treated for 8 weeks. All subjects willing to carry on the study treatment will be able to take part in an open-label study (ABX464-102).

In any other cases, the subjects 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 11 weeks.

4. STUDY POPULATION

4.1. Number of Subjects/Centers

30 subjects will be randomized in this study. These subjects will be enrolled in up to 20 sites located in France, Belgium, Spain, Poland, Germany, Czech Republic, Austria and Hungary.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

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

- Men or women age 18 - 75 years;
- Diagnosis of moderate to severe active UC confirmed by endoscopy and histology at least 12 weeks prior to screening visit. Moderate to severe active UC defined by Mayo Clinic Score (MCS) of 6 to 12 inclusive (on a scale of 0-12). Moderate to severe active UC should be confirmed at screening visit with a centrally read MCS endoscopy score of at least 2 (on a scale of 0-3);
- Subjects 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 (≤9mg/day), for ≥2 weeks before the screening visit;
- Topical corticosteroids and topical 5-aminosalicylic acid preparations must have been withdrawn ≥2 weeks before the screening visit due to inefficacy or intolerance;
- Subjects who are on oral 5-aminosalicylic acid must have been on a stable dose ≥4 weeks before the screening visit;
- Subjects who are receiving immunosuppressants in the form of azathioprine, 6-mercaptopurine, or methotrexate needed to be on a stable dose for 4 weeks before the screening visit. Subjects taking methotrexate also are advised to take folic acid 1 mg/day (or equivalent) supplementation if there is no contraindication;
- Subjects on probiotics (e.g., Culturelle® [Lactobacillus GG, i-Health, Inc.], Saccharomyces boulardii) must be on stable doses for 2 weeks before the screening visit;
- Subjects on antidiarrheals (e.g., loperamide, diphenoxylate with atropine) must be on stable doses for 2 weeks before the screening visit;
- Subjects who have previously received anti-tumor necrosis factor (TNF) therapy or vedolizumab must have discontinued therapy ≥8 weeks before the screening visit due to inefficacy or intolerance;
- Subjects previously treated with cyclosporine or tacrolimus must have discontinued therapy ≥4 weeks before the screening visit due to inefficacy or intolerance;
- Subjects previously treated with tube feeding, defined formula diets, or parenteral alimentation/nutrition must have discontinued treatment 3 weeks before the screening visit;
- Subjects with hematological and biochemical laboratory parameters as follows and within 14 days of baseline:
    - Hemoglobin > 9.0 g dL-1;
    - Absolute neutrophil count ≥ 750 mm^{-3};
    - Platelets ≥ 100,000 mm^{-3};
    - Total serum creatinine ≤ 1.3 x ULN (upper limit of normal);
    - Creatinine clearance > 50 mL min-1 by the Cockcroft-Gault equation within 60 days of entry;

  - Total serum bilirubin < 1.5 x ULN;
  - Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 1.5 x ULN;
- Subjects should be able and willing to comply with study visits and procedures as per protocol;
- Subjects should understand, sign and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures being performed;
- Subjects should be affiliated to a social security regimen;
- Females and males receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 3 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 associated with inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the subject. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle.

4.2.2. Exclusion Criteria

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

- Subject with Crohn's Disease (CD), indeterminate colitis (IC) or presence or history of fistula with CD;
- History of toxic megacolon, abdominal abscess, symptomatic colonic stricture or stoma; history or is at imminent risk of colectomy;
- History or current evidence of colonic dysplasia or adenomatous colonic polyps. Subject with severe gastrointestinal complications; e.g., short bowel syndromes, obstructing strictures, recent or planned bowel surgery, Ileostomy and/or colostomy, recent bowel perforation;
- Subject with significant and known active infections at screening such as infected abscess, positive for Clostridium difficile (stool antigen and toxin), CMV, TB and recent infectious hospitalization;
- Acute, chronic or history of clinically relevant pulmonary, cardiovascular, hepatic, pancreatic or renal functional abnormality, encephalopathy, neuropathy or unstable CNS pathology, angina or cardiac arrhythmias, 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 unless there has been surgical excision that is considered to have achieved cure;
- Active malignancy that may require chemotherapy or radiation therapy;
- Seizure disorder or any history of prior seizure;
- Serious illness requiring systemic treatment and/or hospitalization within 3 weeks prior to baseline;
- Pregnant or breast-feeding woman;
- Active drug or alcohol abuse or dependence;
- Use of any investigational or non-registered product within 3 months preceding baseline;
- Any condition, which in the opinion of the investigator, could compromise the subject's safety or adherence to the study protocol.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1. Study Flow Chart

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

			Study Treatment Period							
	D-14	Randomization	D0	D7	D14	D21	D28	D42	D56	D63-EOS
Time Window	± 3 days			± 2 days	± 2 days	± 2 days	± 2 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	X
Body Weight (kg)	X		X	X	X	X	X	X	X	X
Height Measurement (cm)	X									
Medical History and Concomitant Medications	X									
Vital signs	X		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	
Hematology + Biochemistry	X		X	X	X		X		X	X
Mayo score (Total or Partial)	X		X	X	X	X	X	X	X	X
Faecal calprotectin			X				X		X	X
Rectal microbiota	X								X	
Sigmoidoscopy	X								X	
SF-36 (Questionnaire)			X				X		X	
ABX464/placebo treatment dispensation and subject diary review			X				X			
Blood samples drug pK			X*				X*			
Samples for miRNA (Paxgene tubes)			X				X		X	
Adverse Events recording			X	X	X	X	X	X	X	X

* Applicable to the first 9 subjects randomized / PK predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8 and 12 post-dose

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 (14 ± 3 days prior to Day 0)

The subject will be informed about the general aspects of the study and will sign the screening informed consent form. The subject number will be allocated once the subject will be created in the eCRF. Only when consent has been given may further study procedures be carried out. During the screening phase, the following assessments will be performed:

- Signed informed consent form;
- Demographic data: date of birth and gender;
- Body weight and height;
- Medical history;
- Physical examination and vital signs;
- Hematology and Biochemistry including pregnancy test for all women of childbearing potential;
- 12 leads ECG;
- Sigmoidoscopy with rectal/sigmoidal biospies;
- Rectal Microbiota sampling (Swab);
- Total Mayo Score;
- Clostridium difficile (stool antigen and toxin), CMV, TB;
- Give the "Subject Diary" and instruct the subject how to use it.

- Record all medications received within 3 months prior to baseline and note if the medication is continuing;
- Inclusion/exclusion criteria will be verified globally.

5.2.2. Randomization procedure

The randomization procedure does not require a site visit of the subject. The Investigator needs to check the inclusion/exclusion criteria with respect to the procedures performed at D-14 visit and if applicable proceed with the subject randomization throughout the eCRF.

5.2.3. Baseline (First dosing day / D0)

- SF-36 questionnaire (as the first visit procedure);
- Physical examination and vital signs;
- Body weight;
- 12 leads ECG;
- Pharmacokinetics blood samples (Applicable to the first 9 subjects randomized);
- Hematology & Biochemistry including blood pregnancy test for all women of childbearing potential;
- Blood sample for miR-124 dosage (PAXgene® tube);
- Faecal calprotectin;
- Partial Mayo Score;
- Adverse Events reporting;
- Dispense study treatment to subject and instruct how to take them (First dosing at site);
- Schedule next subject visits.

5.2.4. D7, D14, D21 Visits (± 2 days); D42(± 4 days)

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry (D7 and D14 only);
- Check treatment compliance;
- Review the Subject Diary;
- Partial Mayo Score;
- Adverse Events reporting;
- Schedule next subject visits.

5.2.5. Day 28 (± 2 days) and D56 (± 4 days) Visits

- SF-36 questionnaire (as the first visit procedure);
- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry including blood pregnancy test for all women of childbearing potential;
- Blood sample for miR-124 dosage (PAXgene® tube);
- Pharmacokinetics blood samples (Only at Day 28 visit and applicable to the first 9 subjects randomized);
- 12 leads ECG;
- Faecal calprotectin;

- Sigmoidoscopy with rectal/sigmoidal biopsies only at D56;
- Rectal Microbiota sampling (Swab) only at D56;
- Partial (D28) and Total Mayo (D56) Score;
- Check treatment compliance;
- Adverse Events reporting;
- Study treatment dispensation at Day 28 visit;
- Review the Subject Diary;
- Schedule next subject visits.

5.2.6. End of Study Visits (D63 ± 2 days)

All subjects willing to carry on the study treatment will be able to take part in an open-label study (ABX464-102).

In any other cases, the subjects will perform an End of Study Visit (EoS) within a week after last dosing. Subjects will be treated according to the standard of care since the last day of study treatment.

Following examinations/procedures should be performed:

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry;
- Partial Mayo Score;
- 12 leads ECG;
- Faecal calprotectin;
- Adverse Events reporting.

NB#1: In case of premature discontinuation occurring during the treatment phase (D0-D55), the above examinations should be performed as an End of Study Visit.

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

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

For all female subjects of childbearing potential, a blood pregnancy test (beta human chorionic gonadotropin [HCG]) will be performed at Day -14, Day 0, Day 28, Day 56. In case of positive pregnancy testing, detailed procedures can be found in section 8.3.2.

5.3.3. ECG

Electrocardiograms have to be done at Day -14, Day 0, Day 28, Day 56 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) has to be done in a resting position. Prior to the recording the subject should be at rest for at least five minutes. Resting ECG should be performed before any examinations.

The ECG printout will be reviewed by the investigator and a signed and dated copy of the ECG will be attached to the medical file. The original ECG printouts are considered as source data and should be stored at site. In case thermal paper is used, a copy of the original ECG must be kept as well. All abnormal findings must be documented in the CRF. Any clinically relevant findings compared to ECG done at Day 0 must be documented as adverse events.

5.3.4. SF-36 questionnaire (SF-36)

The SF-36 questionnaire is a self-administered questionnaire containing 36 items which takes about five minutes to complete. It measures health on eight multi-item dimensions, covering functional status, well-being, and overall evaluation of health. SF-36 will be filled in by the subjects at Day 0, Day 28 and Day 56 prior to any study procedures.

5.3.5. Partial/Total Mayo Score

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

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

Either the Partial or the Total Mayo score will be completed at each subject visit by the Investigator.

5.3.6. Sigmoidoscopy with rectal/sigmoidal biopsies

Sigmoidoscopies procedures will be standardized for optimized video acquisition at clinical sites. Sigmoidoscopies should be performed according to the Central Imaging Management System Charter.

Central Imaging Management System will be provided including a central image database. Once uploaded, video data will be analyzed for quality and resolution prior to independent review by an expert central reader.

Study videos will be scored separately using the Mayo Clinic Score for all time points by a single central reader who is blinded to the treatment and visit sequence of the recordings. The central reader's score at Screening and Week 8 will be entered 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 and at Week 8. The two biopsies will be sent to the central laboratory for Geboes score determination (please refer to the lab manual) and for miRNA-124 determination (RNA later).

5.3.7. Hematology and biochemistry

For hematology and biochemistry central laboratory will be used (i.e. Eurofins). All lab dosages will be done centrally except the ESR that need to be done locally. Devices will be anyway provided by Eurofins. Regarding the calprotectin sample, the site will be asked to keep samples at -80°C till the end of the study.

Each laboratory value that is outside of the 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 1 displays the clinical laboratory parameters that must be measured.

Table 1: Laboratory Tests

HEMATOLOGY	BIOCHEMISTRY	STOOLS
Hemoglobin	Sodium	Faecal calprotectin
Hematocrit	Potassium	
WBC	Chloride	
Neutrophils	Calcium	
Lymphocytes	Phosphate	
Monocytes	Glucose	
Eosinophils	BUN or urea	
Basophils	Creatinine	
Platelet count	AST	
ESR	ALT	
	GLDH	
	Lipase	
	Alkaline phosphatase	
	gGT	
	Total bilirubin	
	Total protein	
	Albumin	
	LDH	
	CRP	

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.

5.3.8. 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 whole blood and in tissue will be performed in order to assess treatment effect by comparing before and after treatment. Assays for miRNA determination and tropism test will be conducted by ACOBIOM.

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

5.3.9. Microbiome assays

The microbiome composition might affect the reservoir size and is key to mucosal immunity. Microbiome specimen will be collected using a rectal swab before each flexible sigmoidoscopy procedure. The microbiota will be characterized by ACOBIOM at screening and at Day 56 using 16S rDNA Illumina (R) deep sequencing and analyzed using similar methods.

5.3.10. Pharmacokinetics

The main objective of the PK analysis is to evaluate potential PK specificities of ABX464 in subjects suffering from active UC.

ABX464 was shown to have a very short $t_{1/2}$ (1 to 2 h), so steady-state is virtually reached at the second administration, while NGlcABX464 has a $t_{1/2}$ of 90 to 110 h, meaning that steady-state is reached after 19 to 22 days of administration.

PK analysis will be performed in the first 9 subjects enrolled in this study at Week 0 and Week 4. A first blood sample (reference) will be collected on the first day of treatment before any drug administration then blood samples will be collected for PK purpose at, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8 and 12 post-dose samples

A total of 10 blood samples per subject will be collected for PK purpose and sent to ATLANBIO for Bioanalyses.

Blood samples for determination of ABX464, NGlcABX464, Hydroxyl ABX464 glucuronide and/ will be collected from all subjects using direct venipuncture or an indwelling catheter.

Then, the following PK parameters will be derived for ABX464 and NGlcABX464 for each subject:

- C_{max}, t_{max}: the maximum plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) will be obtained directly from the concentration-time data.
- $AUC_{0-\tau}$: the area under the concentration-time curve from time zero to the time of dosing interval τ (12 h post-dose for ABX464 and NGlcABX464). If no concentration can be measured at this time point, AUC_{0-last} (from time zero to the last quantifiable concentration) will be calculated. Both parameters will be presented independently. For both parameters, a linear trapezoidal method will be used.

Moreover, evaluation of steady-state will be made by visual inspection of the pre-dose concentration measurement collected over the study duration.

5.4. Summary of blood samples

The table 2 below summarizes the volume of blood to be sampled at each study visit.

Table 2: Blood Volume

	REQUIRED VOLUME	COLLECTION TUBE	SCR D-14	BSL D0	D7	D14	D28	D56	EOS D63	TOTAL
Hematology (Hemoglobin, Hematocrit, Red Cell Count, MCV, MCHC, Platelets, White cell count with diff.)	0.5mL EDTA blood	2mL EDTA tube	2	2	2	2	2	2	2	14
Biochemistry panel incl CRP, GLDG and Serum Pregn.	1.5mL serum	3.5mL serum gel tube	3,5	3,5	3,5	3,5	3,5	3,5	3,5	24,5
IL22	1mL serum	2.5mL serum gel tube	2,5	2,5	2,5	2,5	2,5	2,5	2,5	17,5
CMV IgG and IgM	0.75mL serum	2.5mL serum gel tube	2,5							2,5
Quantiferon TB Gold Plus	4mL plasma	4x 1mL tube	4							4
ESR on site	5mL whole blood	5mL ESR tube		5	5	5	5	5	5	30
PK samples	1.0 mL serum	4mL serum tube		40			40			80
miRNA-124 samples	2.5mL whole blood	2.5mL PAXgene tube		2,5			2,5	2,5		7,5
		Total per visit	**14,5**	**55,5**	**13**	**13**	**55,5**	**15,5**	**13**	**180**

6. INVESTIGATIONAL PRODUCT(S)

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

6.1. Description of investigational treatment

The study treatment that will be administrated to subjects enrolled in this Phase IIa study consists of capsules containing ABX464 or its matching placebo given orally once daily for 56 days.

6.2. Description of investigational Product

6.2.1. Active investigational product (ABX464)

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

For the proposed clinical trial, the IMP consists of size 01 capsules containing 50 mg of ABX464 drug substance in the form of granulate prepared with a number of common excipients (microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate and colloidal silica). It is supplied in high-density polyethylene bottles closed with high-density screw caps.

ABX464 will be manufactured by:

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

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

SODIA
Avenue Robert Schuman
51 100 REIMS

The study drug requires no specific storage conditions.

6.2.2. Placebo

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

ABX464 matching placebo will be manufactured by:

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

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

SODIA
Avenue Robert Schuman
51 100 REIMS

The study drug requires no specific storage conditions.

6.3. Administration and Dosing

6.3.1. Administration of the investigational product

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

Subjects will be orally dosed in fed condition (regular breakfast) with 240 mL of water.

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

6.3.2. Guidelines for treatment postponement and dose modifications

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

6.4. Method of Assigning Subjects to Treatment Arms

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

Eligible subjects will be randomized according to a 2/1 ratio to either an ABX464 or the placebo arm if s/he fulfils all inclusion exclusion criteria.

Randomization will be performed via e-CRF. Treatment numbers will be allocated at once.

Study treatment dispensation will be performed twice at Day 0 (30-capsule bottle; 1 bottle of 50 mg) and at Day 28 (30-capsule bottle; 1 bottles of 50 mg). In all cases, subject should return his/her used and unused bottles at each study visit for a compliance check.

6.5. Blinding and breaking the study blind

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

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

Investigator could have access to unblinding only in case of medical emergency via specific envelopes. However, as there is no antidote it is highly unlikely that knowledge of treatment would affect the clinical management of the subject.

6.6. Packaging

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

6.7. Storage

ABX464/Placebo capsules will be shipped to the investigational site at ambient temperature.

No special storage conditions are required.

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

Mandatory and/or allowed Concomitant Medications are:

- ABX464 or its matching placebo administered once daily at 50 mg from Day 0 to Day 56 visit.
- Corticosteroids at stable dose of prednisone or prednisone equivalent ≤20 mg/day during the first 4 weeks of study treatment.
- 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 subject 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.

- Anti-tumor necrosis factor (TNF) therapies.
- Vedolizumab.
- Topical corticosteroids and topical 5-aminosalicylic acid preparations.
- Cyclosporine and tacrolimus.
- Drugs that could interact with ABX464 should be avoided especially the CYP1A2 substrates. The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (Clozapine, theophylline, ropinirol, warfarin and methadone). Please refer to Appendix #1.
- Use of any investigational or non-registered product within 3 months preceding baseline.

7. SUBJECT COMPLETION AND WITHDRAWAL

7.1. Subject Completion

Treatment with ABX464/Placebo shall continue until Day 56 visit, except if a subject fulfils a premature discontinuation criterion (defined below). After Day 56, subjects are willing to carry on the study treatment will be able to take part in an open-label study (ABX464-102).

In any other case, the subjects will exit the study (EoS) and will be treated according to the standard of care. The ABX464-102 follow-up study is a separate clinical protocol subject to health authorities and ethics committee approvals.

7.2. Premature trial discontinuation

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

Subject's premature trial discontinuation could occur for the following reasons:

- Investigator's decision;
- An Adverse Event or an intercurrent condition that preclude continuation of treatment;
    - Specifically, an increase ≥ 2.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT), in Alkaline phosphatase or in total bilirubin should be considered a treatment discontinuation criterion.
- Worsening of the UC defined as a 2-point increase from the screening MCS with 3 days of continuous rectal bleeding confirmed by flexible sigmoidoscopy with an endoscopy subscore of 2 points or higher;
- Major protocol violation;
- Subject's decision;
- Withdrawal of consent;

A subject who prematurely exits the study for a non-drug related reason, will be replaced (i.e. an additional subject will be randomized and receive the next treatment allocation. This may or may not be the same treatment as the withdrawn subject).

7.3. Study Discontinuation

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

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

Based on the investigator evaluation and sponsor prior approval, a non-randomized subject can be re-screened. This re-screening procedure should be documented, the subject should consent again and a new unique and incremental subject 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, only adverse event related to the screening procedures will be collected.

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

8.1. Definition of an AE

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

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

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 subject 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.

8.2. Definition of a SAE

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

a) Results in death

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

b) Is life-threatening

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

c) Requires hospitalization or prolongation of existing hospitalization

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

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

d) Results in persistent or significant disability/incapacity,

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

e) Is a congenital anomaly/birth defect

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

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

8.2.1. Events and/or Outcomes Not Qualifying as SAEs

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

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

8.3. Events or Outcomes Qualifying as AEs or SAEs

8.3.1. Clinical laboratory parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g. vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definitions of sections 8.1 and 8.2 respectively. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at informed consent and significantly worsen during the study will be reported as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, and are present at the start of the study but do not worsen, will **not** be reported as AEs or SAEs. However, if these findings or assessments are judged by the investigator to be more severe than expected considering the subject's condition, then they may be reported as AEs or SAEs.

8.3.2. Pregnancy report

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

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

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

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

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

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

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

SIMBEC ORION

pharmacovigilance@orioncro.com

Fax: +44 (0) 1753 695 101

Legislative guidance requires also reporting any **related** SAEs to be reported after the subject finished the study if the investigator becomes aware of them.

8.5. Recording AEs and SAEs

Severity of AEs will be assessed according to CTC-AE Classification Version 4.0.

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

The following points must be recorded for each event:

- A description of the event in medical terms, not as reported by the subject;
- Date of onset (start date);
- Date of resolution (stop date);
- The time of onset with respect to administering the investigational product;
- The severity of the sign/symptom or clinically significant abnormal laboratory value according to CTC-AE Classification;
- The causal relationship between the investigational product and the occurrence of each AE. This will be assessed by each investigator using clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant medications, other risk factors and the temporal relationship of the event to the investigational product will have to be considered. The causality of all AEs should be assessed by the investigator with the following question: Is there a reasonable possibility that the AE may have been caused by the investigational product? And answered "NO" (if not related) and "YES" (if related);
- Action taken regarding the investigational product:
    - No action;
    - Temporary discontinuation;
    - Permanent discontinuation;
    - Subject's outcome:
    - Recovered without sequelae / resolved without sequelae;
    - Recovered with sequelae / resolved with sequelae;
    - Recovering/Resolving;
    - On-going;
    - Fatal (for SAEs only).

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

8.6. 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 SIMBEC ORION **within 24 hours after knowledge of the event(s).** The SAE forms or paper report forms should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. An assessment of causality should always be provided at the time of the initial report. If the investigator or designee does not have all information regarding the SAE, he/she should not wait to receive additional information before completing the form and notifying SIMBEC ORION.

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

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

8.7. Reporting of SAEs to Regulatory Authorities

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

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

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

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

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

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

9.1. Statistical and Analytical Plans

No interim analysis is planned.

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

9.1.1. Protocol deviations

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

9.1.3. Subjects/Subjects disposition

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

9.1.4. Demographic and other baseline characteristics

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

9.1.5. Treatment compliance

Number of dose intakes 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 terminate the study will be considered failures.

The primary efficacy endpoint of the study, the rate of subjects responding to treatment. This response rate will be compared in subjects who received ABX464 or placebo by stratified likelihood ratio chi-square test on a 10% one-sided level.

In addition, descriptive statistics will be presented by treatment arm for all secondary efficacy variables for each measurement timepoints separately for the two study groups.

These statistics include:

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

- Kaplan-Meier estimates and plots will be presented for time to UC worsening after week 8.
- Mixed model analysis of covariance will be conducted for the following measurements:
    - The change from screening in IL-22 expression levels in serum and rectal/sigmoidal tissue at week 8,
    - The change from baseline in microRNA-124 levels in whole blood (PAXgene®) and in tissue (RNA later) at week 4 and week 8,
    - The change from baseline in fecal calprotectin levels at week 4 and week 8,
    - The change from screening in the histopathology/infiltrate (rectal/sigmoidal biopsies) assessed by the Geboes score at week 8,

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

9.2.1. Pharmacokinetics

A total of 10 blood samples per subject will be collected for PK purpose.

Individual plasma concentrations of ABX464, NGlcABX464, Hydroxyl ABX464 glucuronide, will be presented by treatment and time points. Descriptive statistics for the plasma concentrations will be presented as number of available data (N), mean, standard deviation (SD) and will be calculated if at least 2/3 of the plasma values per time-point are above LOQ (i.e. $N \geq 10$ if 15 subjects are available for a given group). For descriptive statistics calculations, BLQ concentrations below the limit of quantification will be set to zero (0) if they are reported before the first quantifiable sample or considered as missing data if they are reported after the first quantifiable data.

Then, the following PK parameters will be derived for ABX464 and NGlcABX464 for each subject:

C_{max}, t_{max}: the maximum plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) will be obtained directly from the concentration-time data.

$AUC_{0-\tau}$: the area under the concentration-time curve from time zero to the time of dosing interval τ (12 h post-dose for ABX464 and NGlcABX464). If no concentration can be measured at this time point, AUC0-last (from time zero to the last quantifiable concentration) will be calculated. Both parameters will be presented independently. For both parameters, a linear trapezoidal method will be used.

Individual derived PK parameters will be presented by treatment and day of PK assessment when appropriate. Descriptive statistics of the PK parameters will be presented as N, mean, SD, median, minimum (Min), maximum (Max) values, and geometric mean (GM).

In the tables of individual PK parameters, all the deviations from planned analysis will be mentioned by flagging the abnormal results.

Possible exclusion of flagged PK parameters could be performed if, in the judgment of the pharmacokineticist, they are deemed not to be "pharmacokinetically relevant". Exclusion of PK parameters will be discussed in the PK results section. If data are excluded from the PK dataset, all subsequent statistical analyses will be performed twice, once using the complete available PK dataset and once using the final PK dataset as defined by the pharmacokineticist. Study conclusion will be based on the final dataset as defined by the pharmacokineticist.

For each compound, plasma concentration vs. time curves will be presented on a log-linear scale:

- mean plots showing the data of both treatments (administration alone and co-administration with ABX464);
- by subject plots with the treatments on separate plots (spaghetti plots).

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 56;
- Any adverse event which occurs after Day 56.

Adverse events will be described by primary system organ class and preferred term. Numbers and percentage of subjects, and number of occurrence 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.

Analysis of safety will be performed on the safety data set consisting all subjects who received at least one dose of ABX464 in the study.

Primary safety endpoint, the rate of all treatment emergent adverse experiences will be compared between the study groups by stratified likelihood ratio chi-square test on a 10% one-sided significance level.

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

Adverse events will be tabulated (counts and percents) 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 subjects with at least one abnormal values will be tabulated (counts and percents) 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 efficacy endpoint is the rate of subjects responding to treatment. This response rate will be compared in subjects who received ABX464 or placebo by likelihood ratio chi-square test. For the sample size assessment, the following assumptions will be made:

- Response rate (ABX464): 0.6
- Response rate (placebo): 0.2

According to literature the response rate for ABX464 treated subjects is expected to be between 50% and 75% while that in the placebo group is assumed to be approximately 10% to 20% (Gemini 1 study - N Engl J Med 2013; 369:699-710 August 22, 2013).

- Type 1 error: 10% one-sided
- Group allocation rate (ABX464 / placebo): 2:1

If the above assumptions and definitions hold true with a sample size of 30 subjects receiving ABX 464 or placebo in a ratio of 2:1 the study has 81% power to show a difference in response rate between the study groups. To gain more clinical experience with ABX464 in this indication a 2:1 randomization ratio was chosen despite the inevitable loss of power. The actual loss of power with the above assumptions is 4%. Power was computed using the normal approximation method.

Subjects who terminates the study prematurely will be considered failures therefore no adjustment for drop-outs is needed.

Primary safety endpoint is the rate of all treatment emergent adverse experiences. The above sample size is sufficient to detect an increase in general treatment emergent adverse experience rate from 10% to 50% with 86% power by likelihood ratio chi-square test on a 10%, one-sided significance level.

If approximately 20 subjects receive ABX464 the study has 88% chance to detect at least 1 specific treatment emergent AE if the underlying rate of occurrence is 1:10.

When the underlying rate of occurrence is around 1:20 the sample size of 20 subjects is sufficient to observe at least 1 such an event with a probability of 64% in the active treatment group.

10. STUDY CONDUCT CONSIDERATION

10.1. Regulatory and Ethical Considerations

10.1.1. General Requirements

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

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Directive 2001/20/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.

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

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

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

10.1.2. Independent Ethics Committee/Institutional Review Board

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

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

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

10.1.3. Subject Informed Consent

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

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

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

10.1.4. Compensation to Subjects

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

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

11. STUDY MANAGEMENT

11.1. Remote Data Entry

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

Prior to the start of the study, the investigator will complete a "*Investigator site staff signatutre 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 subject medical files should be at the clinical research associate's (CRA) disposal for review.

11.2. Data management

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

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

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

11.3. Data coding

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

11.4. Randomization

Randomization will be centrally managed by block of 3 subjects (2 ABX464/1 placebo). It will be performed via the eCRF. The bottle numbers to be used for a specific subject will be assigned according to a pre-defined randomization list by SODIA. 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 subjects are being protected;
- Check that the data are authentic, accurate, and complete and discuss any inconsistencies;
- Ensure that all study materials are correctly stored and dispensed with particular emphasis to the investigational product;
- Verify that the site staff and facilities continue to be adequate for the proper conduct of the study;
- Ensure that the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements;
- Help resolve any problems that may have arisen.

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

11.6. 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 subjects;
- Approved study protocol and amendments and investigator brochure;
- Treatment accountability;
- Safety reporting;
- Study file;

- Study personnel;
- Log of monitoring visits and monitoring process;
- Medical records and other source documents;
- Site facilities;
- Reports to the IRB/IEC and the sponsor;
- Record retention.

11.8. Study and Site Closure

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

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

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

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

11.9. 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 subjects, as appropriate.

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

The Coordinating Investigator as well as other members of the study committee will be authors on the first publication. The principal investigator of the trial will be the first author. Authorship for other investigators will be assigned on the basis of their recruitment contribution, as well as intellectual and administrative input. Ranking will be according to the number of subjects 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 subjects' medical records) are property of ABIVAX.

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

12. REFERENCES

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13. APPENDICES

Appendix 1: CYPIA2 substrates (in bold: prohibited concomitant medications)

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

Your Health and Well-Being

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

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

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

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

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

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

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

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

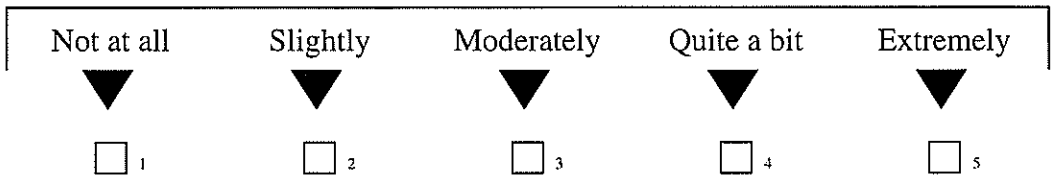
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

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

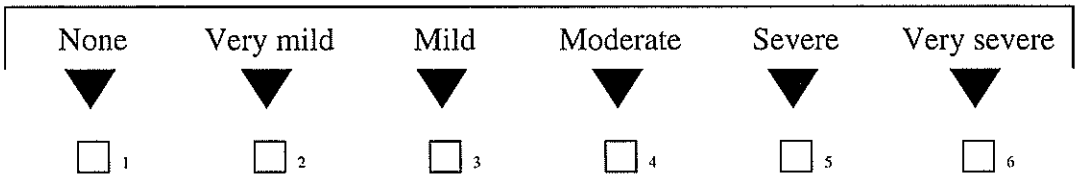
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

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

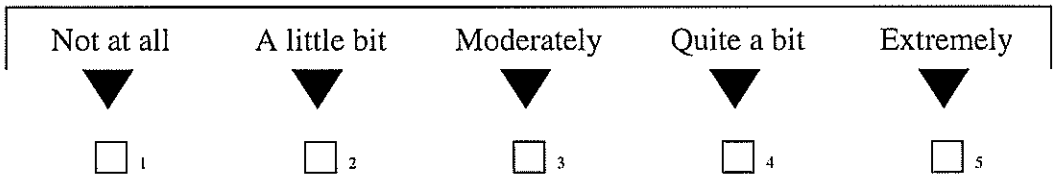
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



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

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

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

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

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

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

Thank you for completing these questions!

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