CLINICAL STUDY PROTOCOL
ABX464-105

Sponsor:	ABIVAX 7-11 Blvd. Haussmann 75009 Paris FRANCE
INN:	Obefazimod
Product code:	ABX464
Therapeutic indication:	Ulcerative Colitis
Study code:	ABX464-105
EU CT number:	[redacted]
IND number:	141396
Phase	3
Protocol title:	A randomized, double-blind, placebo-controlled, multicenter, phase III study to evaluate the efficacy and safety of ABX464 once daily for induction treatment in subjects with moderately to severely active ulcerative colitis
Protocol short title:	ABTECT-1 – ABX464 Treatment Evaluation for ulcerative Colitis Therapy -1
Document version number :	Version 5.1
Version date:	April 10, 2024

CLINICAL STUDY PROTOCOL VALIDATION PAGE

Study code	ABX464-105
EU CT number	[redacted]
IND number	141396
Detailed Title	A randomized, double-blind, placebo-controlled, multicenter, phase III study to evaluate the efficacy and safety of ABX464 once daily for induction treatment in subjects with moderately to severely active ulcerative colitis – ABTECT-1
Document date & version	April 10, 2024 / Version 5.1
Validation	[redacted] MD, Chief Medical Officer: Date
	[redacted] SVP, Regulatory Affairs: Date
	[redacted] Head of Clinical Operations: Date

REVISION HISTORY

Version Number	Impacted Section(s)	Summary of Revisions Made	Rationale
Version 1.0	N/A	Final version of the CSP (not submitted)	N/A
Version 2.0	N/A	Final version of the CSP (used for submission)	N/A
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Version 2.1	Administrative	Change in ABIVAX's address	N/A
[redacted]	[redacted]	[redacted]	[redacted]
Version 3.0	4.2. Exclusion criteria 4.4 Contraception 5.1 Schedule of Assessment 5.3 Detail of the study assessment [redacted] Appendix 7: FACIT-Fatigue [redacted]	Implementation of FDA recommendations	FDA recommendations
[redacted]	[redacted]	[redacted]	[redacted]
Version 3.1	Synopsis 3.1 5.2.4 13.8	Implementation of the Clarification Letter dated 28Nov2022. Correction of Section 5.2.4 accordingly to the Schedule of Assessment (Section 5.1).	Health Canada Agency recommendation
Version 4.0 vs Version 3.0	All	Minor edits were made throughout the document to increase readability and comprehension. A full list of minor edits is not provided.	N/A
	Face page	Updated Company Logo.	N/A
	Validation Page	Updated Signatories.	N/A
	Revision History	Updated Revision History.	N/A

	Contacts	Updated Contacts.	N/A
	Investigator Agreement Page	Updated text.	N/A
	Synopsis	Revisions to reflect implementation of regulatory agency recommendations throughout the protocol	Regulatory Agency recommendations
	1.1 Ulcerative Colitis and Therapeutic Management	Updated and clarified text.	Harmonization and clarity
	1.2 MicroRNA-124 in IBD	Updated and clarified text.	Harmonization and clarity
	1.3 Obefazimod	Updated and clarified text.	Harmonization and clarity
	1.5 Ongoing and Completed Clinical Experience with Obefazimod	Updated clinical data; added Clinical Pharmacology subsection; replaced Table 1.	Accuracy
	1.6 Study Rationale	Updated and clarified text.	Harmonization and clarity
	1.6.1 Dose Selection and Treatment Duration	Updated and clarified text.	Harmonization and clarity
	1.6.2 Study Population	Section moved to 4.1 (Study Population) to align all protocols within the program	Harmonization and clarity
	2.1 Study Specific Definitions	Added and clarified appropriate definitions	Harmonization and clarity
	2.2 Study Objectives and Endpoints	Updated to provide clarity	Clarity and to conform to FDA and EMA guidelines
	3.1 Study Design and Methodology	Updated and clarified text; added description of cardiac biomarker monitoring.	Harmonization and clarity
	3.2 Committees	Added section.	Organization
	3.2.1 IDMC	Updated and clarified text.	Harmonization and clarity
	3.2.2 SSC	Updated and clarified text.	Harmonization and clarity
	[redacted]	Updated and clarified text.	Harmonization and clarity
	3.5 Duration of Study Participation	Updated and clarified text.	Harmonization and clarity
	4 Study Population	Added Section 4.1.	Organization and clarification
	4.3.1 Inclusion Criteria	Updated criterion 1 regarding minimum age.	Regulatory requirements
	4.3.2 Exclusion Criteria	Updated criterion 11 to allow elevated bilirubin with documented Gilbert's syndrome; added criterion 17 regarding acute pancreatitis, 12 regarding hypersensitivity to obefazimod, and 26 regarding institutionalization.	Accuracy
	4.4.2 Prohibited Medications and Procedures	Added subsections on prohibited medications and procedures; updated and clarified text; updated to include S1P modulators and procedures.	Organization and accuracy
	4.5.2 WOCBP	Updated and clarified text.	Harmonization and clarity
	5.1.1 Future Research	Added Section.	Completeness
	5.2 Study Conduct	Updated and clarified text; deleted subsections describing visits.	Harmonization and conciseness
	5.3 Details of Study Assessments	Updated and clarified text in each subsection; deleted RHI scores; decreased biopsy number from 6 to 5, updated Table 4.	Harmonization and conciseness
	6.3 Method of Assigning Subjects to Treatment Arms	Updated and clarified text.	Harmonization and clarity
	6.4 Blinding and Breaking of the Study Blind	Updated and clarified text.	Harmonization and clarity
	6.5 Product Accountability	Updated and clarified text.	Harmonization and clarity
	7 Study Completion	Updated and clarified text.	Harmonization and clarity
	7.1 Subject Completion	Updated and clarified text.	Harmonization and clarity
	7.2 Temporary Treatment Discontinuation	Updated and clarified text.	Clarity

	7.3 Subject Premature Trial Discontinuation	Updated and clarified text.	Harmonization and clarity
	7.4 Screen Failures	Updated and clarified text.	Harmonization and clarity
	7.5 Stopping Rules	Added Section.	Completeness
	8 AEs, SAEs, and AESIs	Added text on incidental findings.	Completeness
	8.1 Definitions	Updated section	Completeness
	8.1.1 Definition of an AE	Added text regarding fluctuations of pre-existing conditions.	Accuracy and completeness
	8.1.2 AESIs	Added text [redacted] Revised text [redacted]	Accuracy and completeness
	8.2 Events and Outcomes Not Qualifying as AES or SAEs	Added text re UC symptoms.	Accuracy and completeness
	8.3.2 Pregnancy Report	Added text regarding stopping treatment.	Accuracy and completeness
	8.5 Time Period and Frequency of Detecting AES, SAEs, and AESIs	Added text regarding pregnancy reports	Accuracy and completeness
	8.7 Reporting of SAEs/AESIs to the Sponsor or its Designees	Updated and clarified text.	Harmonization and clarity
	8.8 Reporting of SAEs to Regulatory Authorities	Updated [redacted]	Completeness
	9.1 Statistical and Analytical Plans	Updated and clarified all subsections.	Harmonization and clarity
	9.2 Safety Analysis	Updated and clarified all subsections.	Harmonization and clarity
	9.3 Efficacy Analysis	Updated and clarified all subsections.	Harmonization and clarity
	9.4.1 Global Study	Updated and clarified text.	Harmonization and clarity
	9.4.2 [redacted]	Updated and clarified text.	Harmonization and clarity
	9.6 PK Analysis	Updated and clarified text.	Harmonization and clarity
	10.2 IRB/IEC	Updated and clarified text [redacted]	Harmonization and clarity
	10.3 Subject Informed Consent	Updated text.	Completeness
	11.6 Randomization	Updated and clarified text.	Harmonization and clarity
	11.11 Study Report and Publication	Updated text.	Completeness
	11.13 Data Protection	Updated and clarified text.	Harmonization and clarity
	13.1 Prohibited Medications	[redacted]	Accuracy
	13.8 [redacted]	Updated and clarified text.	Harmonization and clarity
	13.9 Shipping, Storage and Disposal Arrangements for all Samples Coming from Subjects in the UK	Added section.	Completeness
Version 4.1 vs Version 4.0	Study Title on: Cover Page, Protocol Validation Page, Investigator Agreement Page and initial page of protocol synopsis	Study title changed to substitute INN "obefazimod" with product code "ABX464"	Some countries may not accept introduction of INN in the title for patient-facing materials
	Synopsis, 1.2, 5.3.8	Administrative/typo corrections	Accuracy
	Synopsis & 4.3.2 Exclusion criteria	Administrative / typo correction : "≤15 cm from the anal verge" changed into "<15 cm from the anal verge"	Accuracy
	4.4.2 Prohibited Medications and Procedures	Clarified that non-medicinal procedures are prohibited, regardless of the indication [redacted]	Accuracy

		[redacted]	
	5.3.6 Colonoscopy/Sigmoidoscopy with Rectal/Sigmoidal Biopsies	Updated text, decreased biopsy number from 6 to 5	Clarification
	5.3.8.1. Tuberculosis and QuantiFERON-TB Gold Plus test	Updated text for QuantiFERON-TB gold test positive	Clarification
	8.1.2 AESIs	Updated text [redacted] Removed duplicate text [redacted]	Clarification
	13.6 Appendix 6: Work Productivity and Activity Impairment Questionnaire	Updated wording of question 2	Correction
Version 5.0 vs Version 4.1	All	Minor and administrative edits were made throughout the document to increase readability and comprehension. A full list of minor edits is not provided.	N/A
	Synopsis	Revised to reflect updates throughout the protocol.	N/A
	Synopsis 3.1 Study Design and Methodology [redacted]	Updated text for simplification	Simplification
	1.3.2.3 Obefazimod Reduces Pro inflammatory Lymphocytes and Cytokines/Chemokines	Updated and clarified text	Harmonization and clarification
	1.4 Non-Clinical Background information	Added reference [redacted]	Accuracy
	1.5 Ongoing and Completed Clinical Trials with Obefazimod	Revised section with up-to-date information Updated the number of subjects treated with obefazimod as of 30-November-2023	Accuracy
	1.6.1 Dose selection and treatment duration	Updated the number of subjects treated with obefazimod 50 mg as of 30-November-2023	Accuracy
	2.1 Study-specific Definitions	Clarified definitions	Clarification and accuracy
	2.2.2 Key Secondary Efficacy Objectives and Endpoints	Reworded objectives ('for clinical response' into 'on clinical response')	Clarification
	2.2.3 Other Secondary Objectives and Endpoints	Updated wording for consistency with Section 9.3.3 Analysis of Other Secondary Efficacy Endpoints Clarified the objective and endpoint for concentration of obefazimod and main metabolite	Clarification and accuracy and harmonization
	3.1 Study Design and Methodology	Updated and clarified description of the study design	Clarification and accuracy
	[redacted]	[redacted]	[redacted]
	3.3 Duration of Study Participation	Updated and clarified text	Clarification
	4.1 Study population	Updated and clarified text	Clarification and accuracy
	4.3.1 Inclusion Criteria	Updated and clarified inclusion criteria #1, #3 and #6 Revised criteria #5 regarding inadequate response to previous therapies	Clarification and accuracy
	4.3.2 Exclusion criteria	Updated and clarified exclusion criteria #1, #3, #4, #6, #16, #17 and #22	Clarification and accuracy

	4.4 Allowed and Prohibited Concomitant Medications	Revised for accuracy (extended collection duration to 5 years for conventional therapies)	Accuracy
	4.4.2 Prohibited Medications and Procedures	Updated and clarified the lists of prohibited medications and procedures. [redacted]	Clarification and accuracy
	4.4.3 Transitioning Subjects from Previous Clinical Trials	Updated and clarified text	Clarification and accuracy
	4.5.2 Women of Childbearing Potential (WOCBP)	Clarified wording regarding not recommending true abstinence as a highly effective method of contraception	Accuracy
	4.5.4 Pregnancy Testing	Revised text for simplification	Simplification
	5.1 Schedule of assessments	Updated and clarified Schedule of assessments table and footer notes. [redacted]	Clarification and accuracy
	5.3.3 [redacted]	Clarified text and aligned timepoints and description with Section 13.8, and specific time windows for assessments	Clarification and correction
	5.3.4 Electrocardiogram (ECG)	Updated text for accuracy	Accuracy
	5.3.5 [redacted]	Updated text for accuracy	Accuracy
	5.3.6 Colonoscopy/Sigmoidoscopy with Rectal/Sigmoidal Biopsies	Updated and clarified text	Clarification and accuracy
	5.3.8 Laboratory Parameters	Updated for clarification Added instruction for subjects to arrive in a fed state at the site for study visit. Removed duplicate information regarding drug assays (covered in Section 4.4.2) Revised the list of lab parameters	Clarification and accuracy
	6.1 Description of the Investigational Treatment	Addition [redacted]	Addition
	6.2.1 Administration of the Investigational product	Updated and clarified text	Clarification and accuracy
	6.4. Blinding and Breaking the Study Blind	Added reference to unintentional unblinding	Accuracy
	6.5 Product Accountability	Added reference to partially used treatments	Accuracy
	7.1 Subject Completion	Updated and clarified text	Clarification and accuracy
	7.2 Temporary Treatment Discontinuation	Revised text for clarification	Clarification
	7.3 Subject Premature Trial Discontinuation	Updated and clarified the list of situations in which a subject must be discontinued, and situations in which subject discontinuation will be considered	Clarification and accuracy
	7.4 Screen Failures	Revised text for clarification	Clarification
	8.1.2 AESI	Clarified and revised definitions and reporting criteria for AESIs, to align with obefazimod Investigator's Brochure version 10.0.	Clarified and accuracy

	8.3.1 Clinical Laboratory Parameters and Clinical assessments	Updated and clarified title and text	Clarification and accuracy
	8.3.2 Pregnancy Report	Revised text for simplification	Simplification
	8.5 Time Period, and Frequency of Detecting AEs, SAEs and AESIs	Clarified text	Clarifiation
	8.6 Recording AEs, SAEs and AESIs	Updated and clarified text	Clarification and accuracy
	9.3.1 Analysis of Primary Efficacy Endpoint	Clarified population: 'as defined by inclusion/exclusion criteria' changed to 'who receive at least one dose of study treatment'	Clarification and accuracy
	9.3.2 Analysis of Co-Primary and Key Secondary Efficacy Endpoints (According to EU/EMA Guidance)	Clarified population: 'as defined by inclusion/exclusion criteria' changed to 'who receive at least one dose of study treatment' Added details on the sensitivity analysis	Clarification and accuracy
	9.3.3 Analysis of Other Secondary Efficacy Endpoints	Corrected stratification factor used in ANCOVA	Accuracy
	9.6 PK Analysis	Updated and clarified text	Clarification and accuracy
	9.7 [redacted]	Updated and clarified text	Accuracy
	10.1 General Requirements	Added text related to the collection of race and ethnicity data where allowed by local law	Addition
	11.2 Electronic Data Entry	Updated and clarified title and text	Clarification and accuracy
	11.4 Data Management	Updated and clarified text	Clarification and accuracy
	11.6 Randomization	Changed reference from 'fax or by email' to 'IWRS system'	Accuracy
	11.7 Study Monitoring	Revised text for accuracy	Accuracy
	11.9 Quality Assurance and Inspection by Authorities	Updated and clarified text	Clarification and accuracy
	11.10 Study and Site Closure	Updated and clarified text	Clarification and accuracy
	11.13 Data Protection	Updated and clarified text	Clarification and accuracy
	13 Appendices	Appendix 1 – changed title Appendix 2 – removed questionnaire Appendix 7 – updated and clarified text Appendix 8 – revised for accuracy	Clarification and accuracy Headache questionnaire will be maintained as a separate document from the protocol
Version 5.1 vs Version 5.0	All	Minor and administrative edits were made throughout the document to increase readability and comprehension. A full list of minor edits is not provided.	N/A
	Contacts	Simplified the list of contacts, to keep sponsor and coordinating investigator.	Simplification
	1.4 Non-Clinical Background Information	Updated text for completeness and to align with IB version 10.0.	Consistency and accuracy
	1.3.2.3 Obefazimod Reduces Pro inflammatory Lymphocytes and Cytokines/Chemokines	Updated text for clarification and accuracy.	Clarification and accuracy
	2.2.2 Key Secondary Efficacy Objectives and Endpoints	Removed objective and endpoint linked to symptomatic remission, for FDA and Regulatory authorities other than EMA.	Update
	3.1 Study Design and Methodology	Revised text for Accuracy.	Accuracy
	4.3.2 Exclusion Criteria	Updated exclusion criteria 12.g for clarification. Clarified numbering of criteria #11 and #12.	Clarification and accuracy
	4.4.2 Prohibited Medications and Procedures	Clarified wording [redacted] Removed duplicate wording.	Clarification and simplification

	4.5.4 Pregnancy Testing	Revised text for completeness.	Completeness.
	5.2 Study Conduct	Added text regarding re-consent of minor subjects becoming adult during study participation.	Completeness
	5.3.8 Laboratory parameters	Updated Table 4.	Simplification
	5.3.10 Unexpected Situations and Acceptable Protocol Modifications	Added reference to PK.	Completeness
	6.1 Description of the Investigational Treatment	Changed 'container' to 'blister card'.	Accuracy
	6.5 Product Accountability	Revised text for clarification and accuracy.	Clarification and accuracy.
	7.3 Subject Premature Trial Discontinuation	Updated text for clarification.	Clarification
	8.1.2 AESI	Updated text to align with IB version 10.0 and added clarification.	Clarification and consistency
	8.2 Events and/or Outcomes Not Qualifying as AEs or SAEs	Updated text for clarification.	Clarification
	8.3.2 Pregnancy Report	Revised text for completeness.	Completeness
	8.5 Time Period, and Frequency of Detecting AEs, SAEs and AESIs	Changed the email address used for safety reporting.	Update
	8.7 Reporting of SAEs/AESIs to the Sponsor or its Designee	Updated text for clarification, simplification and accuracy.	Clarification, simplification and accuracy
	9.1.3 Definition of Study Analysis Sets & 9.1.5 Demographic and other Baseline Characteristics & 9.3 Efficacy Analysis & 9.4.1 Global Study	Changed terminology from ITT to FAS.	Accuracy and alignment with ICH guidance
	9.3.1 Analysis of Primary Efficacy Endpoint	Removed reference to symptomatic remission and revised text on sensitivity analysis.	Update
	9.3.2 Analysis of Co-Primary and Key Secondary Efficacy Endpoints (According to EU/EMA Guidance)	Revised text on sensitivity analysis.	Accuracy
	[redacted]	[redacted]	[redacted]
	13 Appendices	Appendix 1 - updated the list of prohibited medications Appendix 8 – removed appendix	Accuracy and simplification

CONTACTS

Sponsor	**ABIVAX** 7-11 Blvd. Haussmann 75009 PARIS - France [redacted] **MBA** CEO, Chief Executive Officer [redacted]
Coordinating Investigators	***For Europe*** **Prof.** [redacted], **MD, PhD** Universitair Ziekenhuis Leuven - campus Gasthuisberg, UZ Herestraat 49 [redacted] Leuven - Belgium ***For US*** **Prof.** [redacted] **MD, MS** Mount Sinai Health System Digestive Disease Institute. 1468 Madison Avenue, [redacted] New York, NY 10029-6574 - USA

INVESTIGATOR AGREEMENT PAGE

EU CT number [redacted]

IND number 141396

Detailed Title A randomized, double-blind, placebo-controlled, multicenter, phase III study to evaluate the efficacy and safety of ABX464 once daily for induction treatment in subjects with moderately to severely active ulcerative colitis.

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

- To conduct the study as outlined in the protocol, any mutually agreed future protocol amendments and with all the terms and conditions set out by the Sponsor.
- 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 Independent Ethics Committee (IEC), Independent Review Board (IRB) 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 current ICH GCP guidelines, the provisions of the Helsinki Declaration, US 21 Code of Federal Regulations dealing with clinical studies, EU Regulation on clinical studies on medicinal products for human use No 536/2014, EU General Data Protection Regulation No 679/2016, or any regional, national or local legislation in force related to clinical studies, or to general data protection.
- 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.

Upon signing the protocol, I agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice (GCP) to which it conforms.

Investigator's Name: _____

Investigator's Signature: _____

Date: _____

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
5-ASA	5-aminosalicylic acid
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT-IR	inadequate response to advanced therapies
[redacted]	[redacted]
β-hCG	beta-human chorionic gonadotropin
BU	bowel urgency
CBC	cap-binding complex
CCL2/MCP1	chemokine for monocytes: monocyte chemoattractant protein-1, mcp-1)
CD	Crohn's disease
CECT	contrast-enhanced computed tomography
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran Mantel Haenszel
CPK	creatine phosphokinase
CRA	clinical research associate
CRO	contract research organization
CRP	C-reactive protein
CS	corticosteroids
CSP	clinical study protocol
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DSS	dextran sodium sulfate
DVT	deep venous thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIM	extra intestinal manifestations
e-Diaries	electronic diary
EM	hospital emergency room

EMA	European Medicines Agency
EoS	End-of-Study
EoT	End-of-Treatment
ePRO	electronic patient-reported outcomes
EQ-5D-5L	Euro Quality of Life–5 Dimensions Questionnaire (5-level)
ER	emergency room
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FC	fecal calprotectin
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
[redacted]	[redacted]
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEMI	histologic-endoscopic mucosal improvement
HEMR	histologic-endoscopic mucosal remission
HIV	Human Immunodeficiency Virus
hsCRP	high sensitivity C-reactive protein
HuMDM	human monocyte-derived macrophages
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonization
[redacted]	[redacted]
IDMC	Independent Data Monitoring Committee
IE	intercurrent event
IEC	Independent Ethics Committee
IL	interleukin
IMID	immune modulated inflammatory disease
IMP	investigational medicinal product
INR	International Normalized Ratio

IR	incidence rate
IRB	Institutional Review Board
IS	immunosuppressants
IV	intravenous(ly)
IWRS	interactive web response system
JAK	Janus kinase
LFT	liver function test
LLN	Lower limit of normal
LTE	long-term extension
[redacted]	[redacted]
[redacted]	[redacted]
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MES	Mayo endoscopic sub-score
miR	micro-ribonucleic acid
miRNA	micro-ribonucleic acid
miR-124	micro-ribonucleic acid 124
MMRM	mixed model for repeated measures
MMS	modified Mayo score
NBM	nocturnal bowel movements
NRI	non-responder imputation
NOAEL	no-observed-adverse-effect level
NRS	numeric rating scale
[redacted]	[redacted]
[redacted]	[redacted]
OC	observed cases
OR	odds ratio
PBD	prevention of blindness and deafness
PBL	prevention of blindness
PBMC	peripheral blood mononucleated cells
PD	progressive disease
PK	pharmacokinetics
PMI	placebo multiple imputation
pMMS	partial modified Mayo score
Pop PK	population pharmacokinetics
PRO	patient-reported outcome
QD	once daily

RA	rheumatoid arthritis
RBS	Rectal Bleeding Sub-Score
RNA	ribonucleic acid
S1P	sphingosine 1-phosphate
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	standard deviation
SFS	Stool Frequency Sub-Score
SEM	standard error of the mean
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SOC	System Organ Class
SSC	Study Steering Committee
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TdP	torsade de pointe
TEAE	treatment emergent adverse event
Th	T helper
TMF	trial master file
TNF	tumor necrosis factor
UC	ulcerative colitis
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
USPI	United States Prescribing Information
[redacted]	[redacted]
[redacted]	[redacted]
VAS	visual analogue scale
WHO	World Health Organization
WOCBP	women of childbearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire

SYNOPSIS

Study n°	ABX464-105	**Clinical Phase**	3
Type of Study	Efficacy, Safety, Tolerability Study		
Study title	A randomized, double-blind, placebo-controlled, multicenter phase III study to evaluate the efficacy and safety of ABX464 once daily for induction treatment in subjects with moderately to severely active ulcerative colitis		
Short title	ABTECT-1 – ABX464 Treatment Evaluation for ulcerative Colitis Therapy -1		
Study centers	Approximately 350 sites located worldwide will participate in the study. (List of potential countries: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, China, Czech Republic, France, Germany, Greece, Hungary, India, Italy, Korea, Netherlands, Poland, Portugal, Spain, Switzerland, Turkey, UK, Ukraine, USA)		
Study Duration	Recruitment period: Q3 2022 – Q4 2024 (approx. 26 months) Overall Study period: Q2 2022– Q1 2025 (approx. 33 months)		
Study Drug Obefazimod	ABX464 (obefazimod) is an oral, first-in-class, small molecule with a novel anti-inflammatory mechanism of action that specifically enhances the expression of the micro-RNA (miR)-124 and initiates anti-inflammatory downstream effects in preclinical animal models and in humans. miR-124 is a critical modulator of immunity and inflammation. miR-124 exerts a crucial role in the development of the immune system, and in the regulation of immune responses (through directly binding of the 3'UTR of monocyte chemoattractant protein-1 (MCP-1) to dampen inflammation, by affecting macrophage polarization via MCP-1 downregulation, and by mediating the cholinergic anti-inflammatory action by inhibiting the production of pro-inflammatory cytokines). Overexpression of miR-124 inhibits intestinal inflammation by attenuating the production of interleukin (IL)-6 and tumor necrosis factor (TNF)-α converting enzyme through the targeting of signal transducer and activator of transcription 3 (STAT3) mRNA. The role of miR-124 is essential in inflammatory disorders such as inflammatory bowel diseases (IBD) (ulcerative colitis [UC]) and Crohn's disease [CD]) and rheumatoid arthritis (RA). Based on data obtained up to 30 November 2023, 1082 subjects have received obefazimod, according to various administration schedules, in all completed and ongoing open-label clinical studies across all indications, including 248 subjects for longer than 6 months and 226 subjects for longer than one year. Additionally, 146 subjects included in the ABTECT program (Phase 3 studies ABX464-105, ABX464-106 and ABX464-107) have received blinded investigational medicinal product (IMP) (obefazimod or placebo).		
Study-specific definitions	For the purpose of the study, the following definitions will be applied: Baseline is defined as the last non-missing assessment performed prior to first dose of study drug, unless stated otherwise. Modified Mayo Score (MMS) is defined as the sum of 3 component scores: Rectal bleeding subscore (RBS), Stool Frequency subscore (SFS) and Mayo Endoscopic subscore (MES). Partial Modified Mayo Score (pMMS) is defined as combination of RBS and SFS. Total Mayo Score (TMS) is defined as the sum of 4 component scores: RBS, SFS, MES and Physician's Global Assessment subscore (PGA).		

Study n°	ABX464-105 **Clinical Phase** 3
	Clinical remission is defined as SFS = 0 or 1 and RBS = 0, and MES = 0 or 1 (MES of 1 modified to exclude friability). Clinical response is defined as a reduction from baseline in MMS ≥ 2 points and a relative reduction from baseline in MMS ≥ 30%, and a reduction from baseline in RBS ≥ 1 point and/or RBS = 0 or 1. Partial Clinical response per pMMS is defined as a reduction from baseline in pMMS ≥ 1 points and a relative reduction from baseline in pMMS ≥ 30%, and a reduction from baseline in RBS ≥ 1 point and/or RBS = 0 or 1. Symptomatic remission is defined as SFS = 0 or 1 and RBS = 0. Endoscopic improvement is defined as MES = 0 or 1 (MES of 1 modified to exclude friability). Endoscopic remission is defined as MES = 0. Histologic improvement is defined as Geboes Index score ≤ 3.1. Histologic remission is defined as Geboes Index score < 2.0 (no neutrophils or eosinophils in lamina propria or in epithelium, no erosion, no ulceration). Histologic-endoscopic mucosal improvement (HEMI) is defined as endoscopic improvement associated with histologic improvement per Geboes scoring. Histologic-endoscopic mucosal remission (HEMR) is defined as endoscopic remission associated with histologic remission per Geboes scoring. Conventional therapies include oral 5-ASA and sulfasalazine, oral or injectable corticosteroids (CS) and immunosuppressants (IS). Advanced therapies (AT) include biologics and biosimilars (anti-TNF [e.g., adalimumab, infliximab, golimumab], α4β7 anti-integrins [e.g., vedolizumab], anti-IL12/23 [e.g., ustekinumab, mirikizumab]), S1P receptor modulators (e.g., ozanimod, etrasimod), and JAK inhibitors (e.g., tofacitinib, filgotinib, upadacitinib) and potential new approved drugs. Nocturnal Bowel Movement (NBM) is defined as one or more sleep interruptions due to a bowel movement. Bowel Urgency (BU) is defined as a sudden, almost uncontrollable need to go to the toilet due to bowel movement. Extra Intestinal Manifestations (EIM) are defined as ocular manifestations (uveitis, scleritis, episcleritis), rheumatological manifestations (axial spondyloarthritis, peripheral spondyloarthritis, arthralgia) or dermatological manifestations (psoriasis, pyoderma gangrenosum, erythema nodosum). Inflammatory Bowel Disease Questionnaire (IBDQ) response is defined as an increase of IBDQ total score ≥ 16 from Baseline. IBDQ remission is defined as an IBDQ total score ≥ 170.
Study Objectives and endpoints	**Primary Objective and endpoint:** The primary/co-primary and key secondary efficacy endpoints will be analyzed separately for FDA and National Regulatory Authorities other than EMA. ▪ For the FDA and National Regulatory Authorities other than EMA purposes, the primary efficacy objective is to compare the efficacy of obefazimod versus placebo on clinical remission defined as: o *Proportion of subjects in clinical remission at Week 8.*

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- For the EMA purposes, the primary efficacy objective is to compare the efficacy of obefazimod versus placebo on endoscopic improvement and symptomatic remission. The co-primary endpoints are defined as:
  - *Proportion of subjects who achieve endoscopic improvement at Week 8*
  - *Proportion of subjects with symptomatic remission at Week 8.*

Key secondary efficacy objectives and endpoints

For the FDA and National Regulatory Authorities other than EMA, the key secondary efficacy objectives and endpoints are:

- To compare the efficacy of obefazimod versus placebo on endoscopic improvement.
  - *Proportion of subjects who achieve endoscopic improvement at Week 8.*
- To compare the efficacy of obefazimod versus placebo on clinical response
  - *Proportion of subjects with clinical response at Week 8.*
- To compare the efficacy of obefazimod versus placebo on HEMI.
  - *Proportion of subjects with HEMI per Geboes scoring at Week 8.*

For the EMA, the key secondary efficacy objectives and endpoints are:

- To compare the efficacy of obefazimod versus placebo on clinical remission.
  - *Proportion of subjects who achieve clinical remission at Week 8*
- To compare the efficacy of obefazimod versus placebo on clinical response
  - *Proportion of subjects with clinical response at Week 8.*
- To compare the efficacy of obefazimod versus placebo on HEMI.
  - *Proportion of subjects with HEMI per Geboes scoring at Week 8.*

Other secondary objectives and endpoints:

- To compare the efficacy of obefazimod versus placebo on MMS.
  - *Change from baseline in MMS at Week 8.*
- To compare the efficacy of obefazimod versus placebo on pMMS.
  - *Change from baseline in pMMS by visit.*
- To compare the efficacy of obefazimod versus placebo on partial clinical response.
  - *Proportion of subjects with partial clinical response by visit.*
- To compare the efficacy of obefazimod versus placebo on RBS.
  - *Proportion of subjects with RBS = 0 by visit.*
- To compare the efficacy of obefazimod versus placebo on SFS.
  - *Proportion of subjects with SFS = 0 or 1 by visit.*
- To compare the efficacy of obefazimod versus placebo on Bowel Urgency (BU).
  - *Proportion of subjects with BU = 0 by visit in the subpopulation of subjects with BU at baseline.*
- To compare the efficacy of obefazimod versus placebo on Fecal Calprotectin (FC).
  - *Change from baseline in FC by visit.*
  - *Proportion of subjects with FC below 150 µg/g by visit.*
- To compare the efficacy of obefazimod versus placebo on Fatigue Numeric Rating Scales (NRS).
  - *Change from baseline in the fatigue NRS by visit.*
- To compare the efficacy of obefazimod versus placebo on FACIT-Fatigue questionnaire.
  - *Change from baseline in the FACIT-Fatigue at Week 8.*
- To compare the efficacy of obefazimod versus placebo on histologic improvement.

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- *Proportion of subjects who achieve histologic improvement per Geboes scoring at Week 8.*

- To compare the efficacy of obefazimod versus placebo on endoscopic remission.
  - *Proportion of subjects who achieve endoscopic remission at Week 8.*
- To compare the efficacy of obefazimod versus placebo on histologic endoscopic mucosal remission (HEMR).
  - *Proportion of subjects with HEMR per Geboes scoring at Week 8.*
- To compare the efficacy of obefazimod versus placebo on histologic remission.
  - *Proportion of subjects who achieve histologic remission per Geboes scoring at Week 8.*
- To compare the efficacy of obefazimod versus placebo on IBDQ.
  - *Change from Baseline in IBDQ total score and domain subscores at Week 8.*
  - *Proportion of subjects with IBDQ response at Week 8.*
- To compare the efficacy of obefazimod versus placebo on nocturnal bowel movement (NBM).
  - *Proportion of subjects with no more NBM by visit in the sub-population of subjects with NBM at baseline.*
- To compare the efficacy of obefazimod versus placebo on Extra Intestinal Manifestations (EIM).
  - *Proportion of subjects with no EIM at Week 8 in the subpopulation of subjects having EIM at baseline.*
- To compare the efficacy of obefazimod versus placebo on symptomatic remission.
  - *Proportion of subjects with symptomatic remission by visit.*
- To compare the efficacy of obefazimod versus placebo on EQ-5D-5L.
  - *Change from baseline in EQ-5D-5L score by visit.*
- To compare the efficacy of obefazimod versus placebo on hsCRP.
  - *Change from baseline in hsCRP by visit.*
- To compare the efficacy of obefazimod versus placebo in WPAI.
  - *Change from baseline in WPAI:UC score at Week 8.*
- To compare the efficacy of obefazimod versus placebo on any UC related Emergency Room (ER) visits, hospitalizations and/or surgery.
  - *Proportion of subjects with UC related visits to ER, hospitalizations and/or surgery.*
- To compare the effect of obefazimod versus placebo on miR-124 expression in tissue and in blood.
  - *Change from baseline in miR-124 expression in rectal/sigmoidal biopsies at Week 8 and in blood by visit.*
- To compare the effect of obefazimod versus placebo on proinflammatory cytokine plasma concentrations.
  - *Change from baseline in proinflammatory cytokine plasma concentrations by visit.*
- To assess the concentration of obefazimod [redacted]
  - *Plasma concentrations of obefazimod [redacted] at baseline, Week 4 and Week 8 (at specified time points depending on the group allocated via IWRS).*

Safety objective and endpoints:

- To evaluate the safety profile of obefazimod versus placebo during induction:
  - *Incidence of all treatment-emergent adverse events (TEAEs), causally related TEAEs, all serious TEAEs and causally related serious TEAEs classified by severity.*

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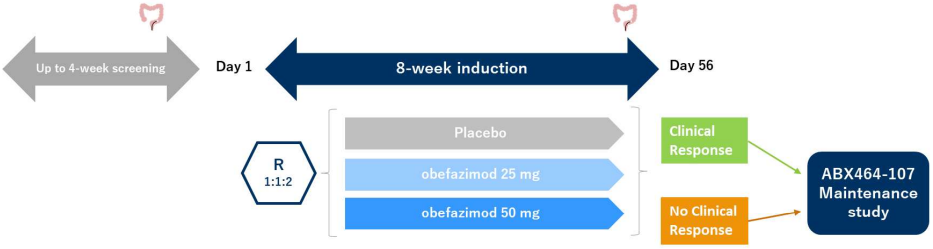
	○ *Incidence of TEAEs leading to investigational medicinal product (IMP) discontinuation and study discontinuation.* ○ *Incidence of treatment-emergent adverse events of special interest (AESIs).* ○ *Incidence of clinically significant laboratory abnormalities.* ○ *Incidence of clinically significant abnormalities regarding vital signs and electrocardiograms (ECGs).* [redacted]		
Study Design and Methodology	This induction study is a multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of obefazimod given at 25 or 50 mg QD in inducing clinical remission in subjects with moderately to severely active ulcerative colitis who have inadequate response (lack of response, loss of response, or intolerance) to either conventional therapies and/or advanced therapies. As shown below, this study consists of a screening period of up to 4 weeks, an 8-week induction period followed by 4-week follow up period. Subjects who complete the 8-week induction will be given the opportunity to take part in the maintenance study (i.e., ABX464-107) either: ▪ In the randomized double-blind placebo-controlled study part [Part 1; placebo, obefazimod 25 mg, obefazimod 50 mg] for clinical responders at Week 8. ▪ In the double-blind multi-arm study part [Part 2; obefazimod 25 mg or obefazimod 50 mg] for non-clinical responders at Week 8. Parts 1 and 2 will last up to 44 weeks. Eligible subjects will then be offered the option to continue in the long-term extension phase of this study for up to 4 additional years or until the commercialization of obefazimod, whichever occurs first. Approximately 612 subjects, will be randomized in this induction study. On Day 1, eligible subjects will be randomized and allocated into three treatment arms according to ratio 1:1:2 as follows: ▪ Placebo: 153 subjects ▪ Obefazimod – Daily dose 25 mg QD: 153 subjects ▪ Obefazimod – Daily dose 50 mg QD: 306 subjects <u>Study design</u>  		

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Randomization will be stratified according to the following factors:

- Subjects with inadequate response to advanced therapies [AT-IR subjects] (lack of response, loss of response or intolerance to advanced therapies (Yes/No)
- Subjects with concomitant oral corticosteroids at baseline (Yes/No)

Approximately [redacted] should have inadequate response to Advanced Therapies. [redacted]

Previous discontinuation of an advance therapy for any reason other than inadequate response, e.g., pregnancy, economic reasons or termination of a clinical trial, will not be considered as AT-IR. In addition to the on-site visit on Day 1 (randomization day), onwards, subjects will be seen at the investigational site at Week 4 and Week 8 according to the study schedule of assessments.

Subjects will also be provided with the direct phone number of the investigational site (i.e., patient card) in order to call the investigator in case UC symptoms are worsening between on-site visits. Subjects will be evaluated for safety and efficacy throughout the induction study.

During the screening period, a full colonoscopy will be performed for all subjects unless one has been performed within the last 3 months before screening. The following information must be noted in the local endoscopic report: UC extension, lack of colonic cancer, lack of low grade or high grade dysplasia adenomatous polyps (fully removed or not). At Week 8, only a flexible sigmoidoscopy is required. At screening and Week 8, during both endoscopic procedures, biopsies will be performed at the most severely affected area. Endoscopies will be centrally read. Sigmoidoscopy might be substituted by a full colonoscopy if requested by national medical practices and/or guidelines. Biopsies will be centrally analyzed.

e-Diaries will be used to collect stool frequency, rectal bleedings, nocturnal bowel movements, bowel urgency and fatigue NRS on a daily basis, as well as whether the subjects took the study treatment and the intake time.

PK samples will be collected [redacted] Subjects will be allocated into two different groups via IWRS. At each time point collection (D1, D28, D56) samples will be taken as follows:

- for group 1: pre-dose, 0.5, 1.5, 3 h (and 6 h and/or 10 h if possible) post-dose
- for group 2: pre-dose, 1, 2, 4 h (and 8 h and/or 12 h if possible) post-dose

A time window of ± 10 minutes is allowed for each time point collection.

[redacted]

[redacted]

At Week 8, subjects who meet eligibility criteria will be given the choice to either take part in the maintenance (ABX464-107) study or to end their participation in the present induction study by completing the end of study visit (4 weeks after the

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	last study drug intake). However, subjects who are eligible for the ABX464-107 study should be encouraged to enter it.
Number of subjects	Approximately 612 subjects will be randomized in this study.
Selection criteria	**Inclusion criteria:** A subject will be eligible to participate in this study if ALL the following criteria are met: 1. Male or female (at birth) at least 16 years old, except in European Union (EU)/European Economic Area (EEA) and Ukraine, where subjects must be at least 18 years old at the time of eligibility assessment. Where enrolment of adolescent subjects is allowed, adolescent subjects must weigh ≥ 40 kg and meet the definition of Tanner Stage 5 at screening. 2. Subjects must understand, sign and date the written voluntary informed consent form at the visit prior to any protocol-specific procedures. For under-aged subjects, national requirements regarding consent should also be met. 3. Documented diagnosis of UC confirmed by endoscopy and histology. Should endoscopy/histology results not be available at screening, results from endoscopy and biopsies taken at screening may be used. 4. Active disease defined by modified Mayo score (MMS) ≥ 5 with rectal bleeding subscore (RBS) ≥ 1 and endoscopy subscore (MES) of 2 or 3 (confirmed by central reader). 5. Subjects with documented inadequate response (defined as lack of response, loss of response and/or intolerance) to at least one of the following treatments: corticosteroids (CS), immunosuppressants (IS), biologic or biosimilar therapies, S1P receptor modulators, JAK inhibitors and/or new drugs approved during the study (note: inadequate response to only 5-ASA or sulfasalazine is not accepted). a. Inadequate response to CS is defined as: i. CS resistance (i.e., signs and symptoms of persistently active disease despite current or prior course of equivalent prednisone/prednisolone ≥ 40 mg/d for at least 2 weeks, or to budesonide ≥ 9 mg/d for at least 2 weeks, or to beclomethasone ≥ 5 mg/d for at least 2 weeks); ii. CS dependence: 1. failure to taper to ≤ 10 mg of equivalent prednisone/prednisolone, < 9 mg/d of budesonide or < 5 mg of beclomethasone; 2. relapse occurring within 3 months after stopping CS; 3. exposure to corticosteroids > 4 months; iii. Intolerance to CS including (but not limited to) Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection. b. Inadequate response to IS is defined as: i. Signs and symptoms of persistently active disease despite azathioprine treatment ≥ 1.5 mg/kg/day for at least 8 weeks, or mercaptopurine ≥ 0.5 mg/kg/day for at least 8 weeks, or methotrexate ≥ 12.5 mg/week for at least 8 weeks; ii. Intolerance to IS including (but not limited to) nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, infection. c. Inadequate response to biologics or biosimilars (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, mirikizumab) is defined as: i. Lack of response to an induction course;

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ii. Loss of response or recurrence of symptoms during maintenance course following primary response after induction course (discontinuation despite clinical benefit does not qualify);

iii. Intolerance to biologics or biosimilars including (but not limited to) infusion-related reaction, serious opportunistic infection, malignancies.

d. Inadequate response to JAK inhibitors (tofacitinib, filgotinib, upadacitinib) is defined as:

i. Lack of response to an induction course;

ii. Loss of response or recurrence of symptoms during maintenance course following primary response after induction course (discontinuation despite clinical benefit does not qualify);

iii. Intolerance to JAK inhibitor treatment including (but not limited to) increase of serious infection, malignancies, deep venous thrombosis (DVT), or major adverse cardiac event (MACE).

e. Inadequate response to S1P receptor modulators (ozanimod, etrasimod) is defined as:

i. Lack of response to an induction course;

ii. Loss of response or recurrence of symptoms during maintenance course following primary response after induction course (discontinuation despite clinical benefit does not qualify);

iii. Intolerance to S1P receptor modulators including (but not limited to) serious infections, liver enzyme, cardiac abnormalities, lymphopenia.

f. Lack of response, loss of response or intolerance to any new drug approved for moderate to severe active UC during the course of the study.

6. Women of childbearing potential (WOCBP) subjects and male subjects with WOCBP partner must agree to comply with contraception requirements as described in Section 4.5 of this protocol.
7. Subjects able and willing to comply with study visits and procedures as per protocol.
8. Subjects should be affiliated to a health insurance policy whenever required by a participating country or state.

Exclusion Criteria:

Subjects who meet ANY of the following exclusion criteria will be excluded from the study:

1. Subjects with UC limited to an isolated proctitis (<15cm from anal verge) determined by endoscopy central reading.
2. Subjects with primary sclerosing cholangitis or autoimmune hepatitis.
3. Subjects who had inadequate response to 5-ASA or sulfasalazine therapy only.
4. Subjects with CD, presence or history of fistula, indeterminate colitis, infectious/ischemic colitis or microscopic colitis (lymphocytic and collagenous colitis).

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	5. History or current evidence of toxic megacolon, fulminant colitis, bowel perforation. 6. History of colonic cancer or colonic low grade or high grade dysplasia adenomatous polyps, and/or at the screening endoscopy, evidence of colonic cancer or evidence of low grade or high grade dysplasia adenomatous polyps (fully removed or not). 7. Recent or planned bowel surgery or history of proctocolectomy or partial colectomy or current stoma. 8. Subjects on antidiarrheals including those working on motility (e.g., loperamide, diphenoxylate with atropine, etc.). 9. Subjects on probiotics (e.g., Culturelle® [Lactobacillus GG, i-Health, Inc.], *Saccharomyces boulardii*). 10. Subjects who do not meet the washout period requirements prior to the screening endoscopy as described in the prohibited medication section (Section 4.4.2) of the study protocol. 11. Subjects with the following hematological and biochemical laboratory parameters obtained during the screening period: a. Hemoglobin ≤ 8.0 g dL^{-1} b. Absolute neutrophil count < 750 mm^{-3} c. Platelets < 100,000 mm^{-3} d. Creatinine clearance < 60 $mL.min^{-1}$ (Cockroft-Gault formula) e. Total serum bilirubin > 1.5 x ULN (except if related to pre-existing and documented Gilbert syndrome) f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x ULN 12. Subjects with the following conditions (infection): a. Subjects with chronic or recurrent grade 3 or grade 4 infection within the last 2 months prior to screening or a history of opportunistic infection while not on immunosuppressive therapy. b. Herpes zoster reactivation within the last 2 months prior to screening. c. Subjects with active infection at screening or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 1 month of screening or during screening. Fungal infection of nail beds is allowed. d. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or positive test for Clostridium difficile toxins at screening. If C. difficile is positive, subject may be treated and retested ≥ 2 weeks after completing treatment. e. Subjects with HIV infection. f. Subjects having acute or chronic hepatitis B infection at screening (positive for hepatitis B surface antigen [HbsAg], or negative for HbsAg and positive for anti-hepatitis B core antibody in conjunction with detectable HBV DNA, or detectable HBV DNA). g. Subjects having acute or chronic hepatitis C infection at screening as defined by positive for hepatitis C antibody and positive HCV RNA (subjects

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	successfully treated and without recurrence ≥ 1 year with no detectable HCV RNA [assessed centrally] are eligible). h. Active tuberculosis (TB) or untreated latent TB are ruled out. For subjects with positive or intermediate QuantiFERON test see Section 5.3.8.1 of the current study protocol. 13. Subjects with an uncontrolled ischemic heart disease and/or a history of congestive heart failure with New York Heart Association (NYHA) class 3 or 4 symptoms. 14. Subjects with a family or personal history of congenital or acquired long QT syndrome, or subjects with a marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval [Fridericia correction] >450 milliseconds for male and >460 milliseconds for female). 15. Subjects with a history of torsade de pointe (TdP). 16. Acute or chronic clinically relevant pulmonary, hepatic, or renal functional abnormality, encephalopathy, neuropathy, or unstable central nervous system pathology such as seizure disorder, or any other clinically significant medical problems as determined by physical examination and/or laboratory screening tests and/or medical history (note: treated autoimmune hypothyroidism and autoimmune diabetes are allowed). 17. [redacted] 18. History or active [redacted] 19. Serious illness requiring hospitalization within 4 weeks prior to screening (except UC flare). 20. Subjects previously treated with obefazimod. 21. Subjects with a known hypersensitivity to the active substance or to any of the excipients. 22. WOCBP subject who is pregnant or breast-feeding at screening, or intends to become pregnant during the study, or male subject with WOCBP partner who intends to be pregnant during the study. 23. Illicit drug or alcohol abuse or dependence. 24. [redacted] 25. Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer, and during the study. 26. Subjects committed to an institution by virtue of an order issued either by the judicial or the administrative authorities. 27. Any condition, which in the opinion of the investigator, could compromise the subject's safety or adherence to the study protocol.
IMP, Dose, and Mode of administration	Depending on the treatment arm allocation, obefazimod or its matching placebo (capsules) 50 mg and 25 mg are administered once daily in a fed condition (ideally at the same time in the morning) for 8 weeks during the induction phase.

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Medications and Procedures	All previous UC medications on which failure of treatment has occurred will be recorded into the electronic case report form (eCRF) without time limitation for advanced therapies and over the past 5 years for conventional treatments. Previous and current medications will be reviewed to check the use of potentially prohibited medication and ensure appropriate washout period is respected. Any change in concomitant medication will be duly checked at each study visit or by phone by site personnel. All concomitant medications will be recorded into the eCRF. **Allowed Concomitant Treatment:** For the treatment of UC (provided stable dose for at least 2 weeks prior to the screening endoscopy and during the whole induction study), the following medications are allowed upon entry into the study: ▪ CS: prednisone or prednisone equivalent ≤ 15 mg/day; beclomethasone dipropionate (≤ 5 mg/day) or budesonide MMX (≤ 9 mg/day). ▪ Oral 5-ASA. **Prohibited Medications and Procedures:** The following medications and procedures are prohibited from enrollment, throughout the entire study, until study discontinuation. For some of them used prior to subjects' enrollment a strict washout period may apply. Sites are allowed to assay drug levels during the study period to shorten the washout periods. <u>Prohibited Medications:</u> ▪ Initiation of any oral, injectable, or rectal CS, or oral and rectal aminosalicylates and other enemas/suppositories (other than required for endoscopy) is prohibited starting 2 weeks prior to the Screening endoscopy. ▪ Cyclosporine, tacrolimus, mycophenolate mofetil, or thalidomide must be stopped at least 4 weeks prior to Screening endoscopy. ▪ Azathioprine or 6-mercaptopurine or methotrexate must be stopped at least 2 weeks prior to Screening endoscopy. ▪ UC-related antibiotics must be stopped at least 2 weeks prior to Screening endoscopy. ▪ Infliximab, adalimumab, golimumab, anti-TNF biosimilars, ozanimod, mirikizumab must be stopped at least 8 weeks prior to Screening endoscopy. ▪ Vedolizumab and ustekinumab or their biosimilars must be stopped at least 12 weeks prior to Screening endoscopy. ▪ Non-steroidal anti-inflammatory drugs (NSAIDs) must be stopped at least 1 week prior to Screening endoscopy and during the study (except topical NSAIDs and the use of low dose aspirin for cardiovascular [CV] protection or short course [less than 7 days] of NSAIDs for AE treatment). ▪ Traditional medicine (e.g., Chinese medicine) must be stopped at least 2 weeks prior to Screening endoscopy. ▪ Tofacitinib, filgotinib, upadacitinib, etrasimod must be stopped at least 2 weeks prior to Screening endoscopy. ▪ Antidiarrheals and motility agents (e.g., loperamide, diphenoxylate with atropine) must be stopped at least 2 weeks prior to Screening		

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	endoscopy. Any use of antidiarrheals for acute and severe diarrhea must be documented in the dedicated eCRF. ▪ Probiotics, fish oil must be stopped at least 2 weeks prior to Screening endoscopy. ▪ [redacted] ▪ Natalizumab or any other α4β1 integrin agonist: no previous exposure allowed. ▪ Drugs with mechanism of action that may interfere with the assessment of obefazimod efficacy in the treatment of UC (e.g., IL-6 inhibitors, IL-17 inhibitors, anti-CD20). Please systematically refer to your study Medical Monitor. ▪ [redacted] ▪ [redacted] ▪ [redacted] ▪ Any newly approved drug for UC during the study must be stopped at least 5 half-lives prior to Screening endoscopy. ▪ Use of any investigational or non-registered product is prohibited within 3 months or within 5 half-lives preceding baseline, whichever is longer and during the study. ▪ Parenteral or enteral nutrition must be stopped at least 3 weeks prior to Screening endoscopy. <u>Prohibited Procedures</u>: ▪ Total or subtotal colectomy. ▪ Diverting ileostomy, or colostomy. ▪ Any other surgical procedure related to the treatment of UC. ▪ Non-medicinal procedures (e.g., plasmapheresis, cytapheresis, fecal transplantation) regardless of the indication.
Premature trial discontinuation	A subject can be withdrawn at any time from the study. Should a subject discontinue the study early, EOT and EOS visits must be performed as per the SoA (Table 2). Subjects must be discontinued in the following cases: ▪ An adverse event (AE) or any medically significant abnormal laboratory results that would place the subject at risk as determined by Sponsor Medical team and preclude continuation of treatment. ▪ Any relevant toxicity or negative change in the risk/benefit assessment leading to an unacceptable risk for the subject (i.e., occurrence of AEs or unexpected and medically concerning deterioration in condition in terms of its severity or frequency, or otherwise a new occurrence in comparison to those AEs listed in the Reference Safety Information per requirements set out in regulation

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	536/2014 and ICH E2F), or any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment. ▪ [redacted] ▪ Severe (grade ≥ 3) infection, severe or serious opportunistic infection, or sepsis. ▪ [redacted] ▪ [redacted] ▪ Abnormal liver enzymes test as below: o ALT or AST > 8 x ULN. o ALT or AST > 5 x ULN for more than 2 weeks. o ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5. o ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). ▪ Pregnancy. ▪ Subject withdrawal of consent. ▪ Subject significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by investigator and Sponsor Medical team. ▪ Study termination by Sponsor. Subject's premature trial discontinuation will also be considered in the following cases: ▪ Anemia and/or new onset anemia (defined as hemoglobin < 8 g/dL or hemoglobin drops > 2 g/dL from baseline) will be discussed on case-by-case basis with Sponsor Medical team and documented accordingly. Note: transient abnormal values, and/or abnormal values related to an existing condition that do not constitute a medically significant worsening will not be a criterion for discontinuation. ▪ Protocol deviation (including inclusion/exclusion criteria noted after randomization) or introduction of prohibited medications or dosages, as determined by Investigator and Sponsor Medical team. ▪ Investigator's decision that can be made at any time during the course of the study, especially in case of UC lack of effect or loss of effect (symptom worsening). A subject who prematurely exits the study will not be replaced.
Duration of Study	The total study duration for subjects is up to 16 weeks, including: ▪ Up to 4 weeks of screening. ▪ 8 weeks of induction. ▪ 4 weeks of safety follow-up (only for subjects not willing, or not eligible, to enter the maintenance study). The total study duration is 12 weeks for eligible subjects willing to join the maintenance study (ABX464-107) after their participation in study ABX464-105. The total study duration for subjects not willing, or not eligible, to join the maintenance study (ABX464-107) is 16 weeks.
Subject Follow-up	For completed subjects, the last dose of the induction study will be taken on site, the day of the last visit (D56 ± 2 days).

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	Subjects eligible for maintenance will be encouraged to take part in the ABX464-107 study. The first treatment dose taken in the frame of the maintenance study will be taken after the study specific informed consent is signed. Subjects who do not take part in the maintenance study will come for a last safety follow-up visit and will be then followed as per the site standard of care after this last study visit.
Sample Size calculation	A total of 612 subjects (153:153:306) will allow the detection of a difference of at least [redacted] in the clinical remission rate at Week 8 between obefazimod 50 mg (and 25 mg) and placebo with a statistical power of at least [redacted]. This calculation, based on a Chi-square test [redacted] assumes a placebo clinical remission rate of [redacted] Sample size calculations was performed with nQuery, version 7.

Study n°	ABX464-105 **Clinical Phase** 3
Statistical Methods	**Interim analysis**: No interim analysis is planned. **Efficacy:** The primary endpoint for FDA (and National Regulatory Authorities other than EMA) regulatory purposes is clinical remission (based on the modified Mayo Scoring system and is defined as SFS = 0 or 1 and RBS = 0 and MES = 0 or 1 (MES of 1 modified to exclude friability), will be analyzed using a Cochran Mantel Haenszel test (CMH) test adjusting for AT-IR (yes/no) and baseline oral corticosteroid treatment (yes/no) as stratification factors, using the Full Analysis Set (FAS). The co-primary endpoints for EMA regulatory purposes are endoscopic improvement at Week 8 (defined as MES = 0 or 1 [MES of 1 modified to exclude friability]), and symptomatic remission (defined as SFS = 0 or 1 and RBS = 0) at Week 8. [redacted] If comparisons on primary endpoints for each dose are statistically significant, then, the testing procedure will continue through each of the key secondary endpoints in the prespecified order until an endpoint fails to reach statistical significance, after which all subsequent key secondary endpoints will be considered exploratory. [redacted] All intercurrent events will be handled by a composite strategy. Sensitivity analyses, addressing estimand strategies together with the corresponding estimands will be performed. **Safety:** AEs will be tabulated (counts and percentages) by treatment group. All AEs will be listed, and the data will be tabulated by body system/organ class. AE tabulations will include all TEAEs, which will be further classified by severity and relationship to treatment. Clinical laboratory parameters, vital signs, ECGs, [redacted] will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum, and maximum). The number of subjects with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables, by treatment group. **Pharmacokinetics:** A popPK model will be constructed for analysis of PK data.
End of trial definition	If the last subject takes part to the maintenance study: End of Trial will be based on the last visit of the last remaining subject in the induction study. If the last subject does not take part in the maintenance study: End of Trial will be the date of the last follow-up of the last remaining subject. In case the last subject is declared lost to follow-up, the date of the last follow-up or the date of the last contact attempt (whichever occurs later) should be considered as End of Trial.

1 Introduction and Study Rationale

The trial will be conducted in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s) (refer to Section 10 and Section 11 for further details).

1.1 Ulcerative Colitis Disease and Therapeutic Management

Ulcerative colitis (UC) belongs to the group of immune mediated inflammatory diseases (IMIDs) and is characterized by a dysregulated immune response associated with a chronic inflammation of the rectal and colonic mucosa and sub-mucosa layers (1). The cause of UC is unknown but genetic, environmental, and immunologic factors have been proposed as contributing to the inflammatory bowel disease (IBD) pathogenesis (1).

The incidence of UC has reached 23 to 58 per 100,000 in the Western world and is increasing in newly industrialized countries/regions in Asia and Latin America as well as in developing countries (2). In the USA, more than 1 million people are affected. UC is usually diagnosed at the end of adolescence/early adulthood, at a time when people may be students, or in the early stages of their career and/or planning a family. The quality of life for people living with UC may be dramatically impacted from direct physical disabilities to financial burden. Among the population suffering from UC, 66% describe interference with work and 73% with leisure activities (3). By extension, UC burdens immediate family members and affects the quality of life of the family unit. UC is also a burden for society within the USA with an estimated 700,000 physician visits and 100,000 hospitalizations related to UC (4).

Most patients present with mild-to-moderate UC at diagnosis but around one third will worsen to moderately to severely active UC. Patients with moderately to severely active UC were treated only with conventional therapies including 5-ASA, corticosteroids (CS) and immunosuppressants (IS) until 2005 when the first biologic (infliximab) was approved for UC.

Other advanced therapies followed including biologics (tumor necrosis factor (TNF) inhibitors including adalimumab and golimumab, the anti-integrin vedolizumab and the interleukin (IL)12/23 inhibitor ustekinumab) and more recently Janus kinase (JAK) inhibitors including tofacitinib, filgotinib (only approved in Europe) and upadacitinib, and the sphingosine 1-phosphate (S1P) modulators ozanimod and etrasimod. With these advanced treatments, at the end of an induction course of treatment, the percentage of subjects with clinical remission is typically 15-35% (5-12). After 1 year of treatment, among induction treatment clinical responders, clinical remission rates are 35-49% (5-12).

The rates of clinical remission diminish as an individual subject receives and doesn't respond to each successive treatment. Given these relatively low rates of clinical remission in both induction and maintenance studies, despite these available therapies, there is still an unmet medical need for novel treatment options for subjects with moderately to severely active UC, especially for those after failure of biologics, JAK inhibitors and/or S1P modulators (1).

1.2 MicroRNA-124 in IBD

Micro-ribonucleic acid 124 (miR-124) is a physiological modulator of inflammation based on its ability to dampen the expression of a variety of cytokines (13). Enhanced expression of miR-124 reduces the expression of key cytokines (IL6r, STAT3) and chemokines (CCL2/MCP1) involved in inflammatory pathways in IBD resulting in decreased macrophage recruitment and activation and Th17 cell differentiation (13).

1.3 Obefazimod

Obefazimod is an investigational, oral, once-daily, small molecule that selectively enhances the expression of miR-124 and has been shown to initiate anti-inflammatory downstream effects in preclinical animal models and in humans.

In humans, obefazimod is metabolized via glucuronidation to ABX464-N-Glu, which contributes the majority of plasma exposure. ABX464-N-Glu is pharmacologically active and binds, like obefazimod, to the Cap-Binding Complex (CBC) leading to enhanced expression of miR-124.

1.3.1 Description

The chemical name of obefazimod molecule is 8-chloro-N-[4-(trifluoromethoxy) phenyl] quinolin-2-amine, or (8-chloro-quinolin-2-yl)-(4-trifluoromethoxy-phenyl)-amine. Obefazimod has a molecular weight of 338.7 g/mol.

The study drug is formulated as [redacted]

1.3.2 Mode of Action

1.3.2.1 Obefazimod Upregulates MiR-124 *In vitro* in Several Cell Types

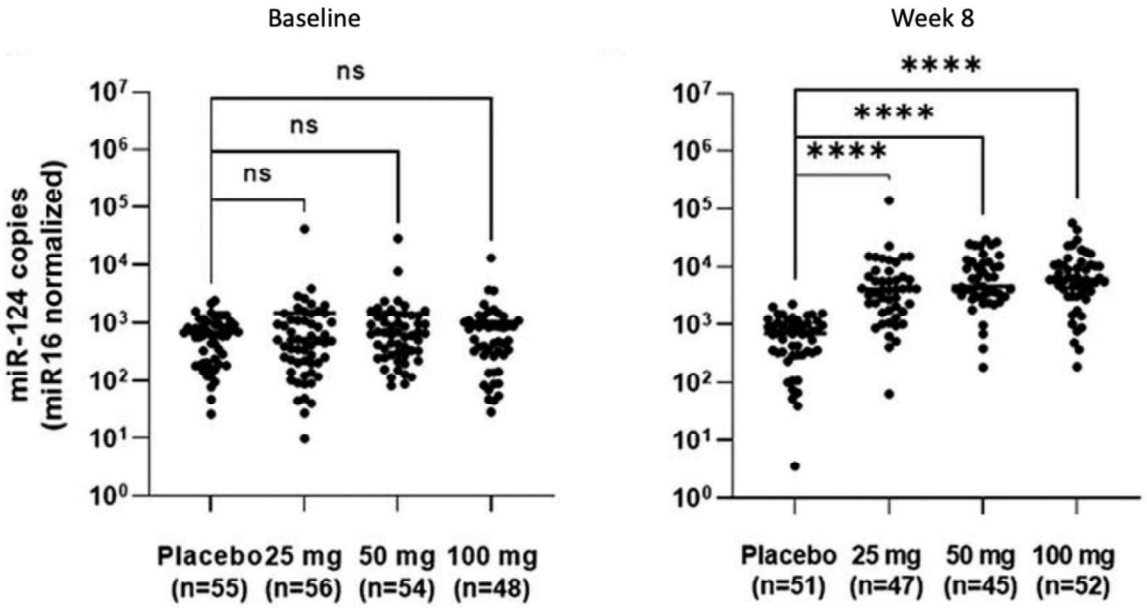
Enhanced expression of miR-124 by obefazimod in human peripheral blood mononucleated cells (PBMCs) has been demonstrated with the following methodologies Affymetrix genechip micro messenger ribonucleic acid (miRNA) array 2.0 and TaqMan® Array Human MicroRNA. Both approaches demonstrated that only miR-124 was upregulated by obefazimod treatment across species and that no miRNAs were downregulated. The expression of miR-124 was markedly increased (about 100-fold) by obefazimod (14). MiR-124 expression was enhanced after obefazimod treatment in both CD4+ and CD8+ T cells (15, 16).

The effects of obefazimod on miR-124 expression was tested in human monocyte-derived macrophages (HuMDM). The results demonstrated that using real-time TaqMan quantitative polymerase chain reaction, obefazimod is able to up-regulate the expression of miR-124 in HuMDM (RSR_INF004).

1.3.2.2 Obefazimod Upregulates MiR-124 in Treated Subjects with Moderate to Severe Ulcerative Colitis

After 8 weeks of treatment (56 days) with obefazimod at doses of 25, 50, or 100 mg, the number of miR-124 copies in rectal biopsies and in blood were significantly higher in all obefazimod groups compared to placebo, as shown in Figure 1 and Figure 2 respectively (RSR_ABX464-103_1, (16)).

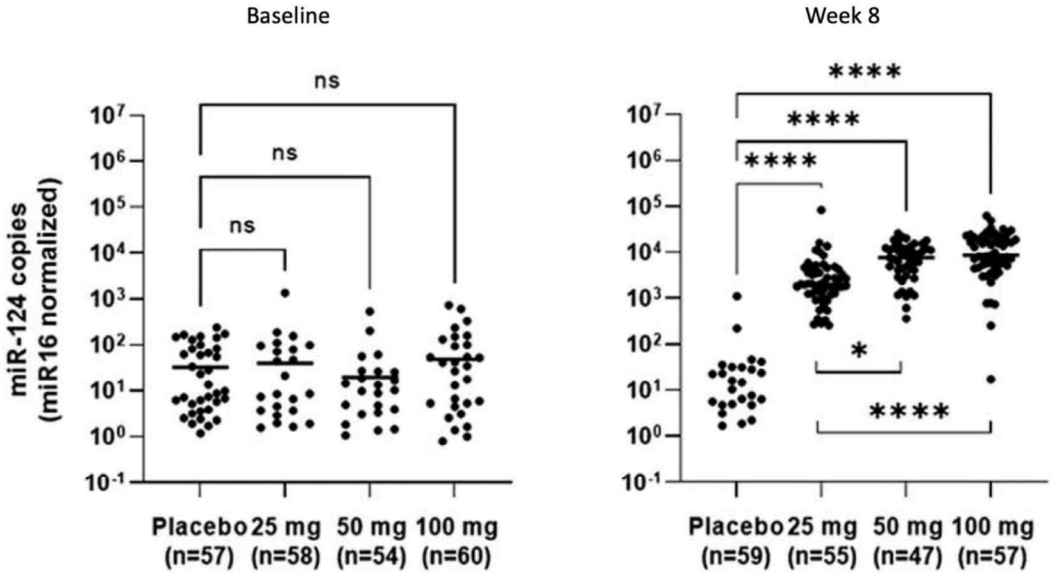
Figure 1: miR-124 Induction in Rectal Biopsies of Subjects Treated with Obefazimod in the Phase 2b trial (UC)



miR-124= micro-ribonucleic acid 124; ns=not significant; UC=ulcerative colitis.

The number of miR-124 copies was assessed by droplet digital PCR at baseline and Week 8. A total of 576 rectal biopsies from 139 subjects who received obefazimod (25 mg, 50 mg or 100 mg) or placebo were analyzed. Kruskal-Wallis test (****P<0.0001 vs placebo).

Figure 2: miR-124 Induction in Blood of Subjects Treated with Obefazimod in the Phase 2b trial (UC)



miR-124= micro-ribonucleic acid 124; ns=not significant; UC=ulcerative colitis.

The number of miR-124 copies was assessed by droplet digital PCR at baseline and Week 8. A total of 1104 blood samples from 229 subjects who received obefazimod (25 mg, 50 mg or 100 mg) or placebo were analyzed. Kruskal-Wallis test (*P<0.05 50 mg vs 25 mg; ****P<0.0001 vs placebo).

1.3.2.3 Obefazimod Reduces Pro-inflammatory Lymphocytes and Cytokines/Chemokines

Lymphocytes T helper 17 (Th17) and the related cytokines, including IL-17, IL-23, and IL-22, are often increased in the inflamed intestinal mucosa of active UC and Crohn's disease (CD) subjects relative to unaffected regions and healthy controls (8). Treatment of PBMCs by obefazimod decreased the number of Th17 and Th1 cells without affecting the regulatory T cell (Treg) populations (16). Obefazimod also reduced the expression of pro-inflammatory chemokines/cytokines monocyte chemoattractant protein-1 (MCP-1, -34%), IL-10 (-90%), IL-1β (-25%), TNFα (-25%) and IL-6 (-90%) within 4 days of treatment of HuMDM polarized to M1 phenotype (16).

In vivo evidence for the role of obefazimod in inflammation is as follows:

Obefazimod decreases pro-inflammatory cytokines.

The results observed in vitro were confirmed in vivo in the mouse model of dextran sulfate sodium (DSS)-induced colonic inflammation (16). Treatment with obefazimod significantly reversed the increases of several proinflammatory cytokines induced in mouse colon by DSS (granulocyte-macrophage colony-stimulating factor [GM-CSF], IL-10, IL-34, TPO, LIF, CXCL12, IL-6, and CCL2) and maintained their levels close to those of healthy mice. Obefazimod also tended to reverse DSS-induced changes for IL-17a, IL-22, SCF, GM-CSF, and IL-1a (17).

Obefazimod decreases the pro-inflammatory TH17 CD4+ cell subset.

In mice, mesenteric lymph nodes contribute to proinflammatory Th17-cell generation during inflammation in the small intestine. Th17 cells are known to differentiate in response to pro-inflammatory IL-1β, IL-6 and IL-23 through signal transducer and activator of transcription 3 (STAT3) pathway, one of the targets of miR-

124 (4). Obefazimod treatment reversed the DSS induced upregulation of IL-17a-secreting cells and maintained them at a level equivalent to that in healthy mice (16).

Obefazimod reduces disease severity in an acute DSS-induced colitis model.

Compared to untreated mice, a reduced DSS-induced weight loss was observed in mice receiving obefazimod. The weight of obefazimod-treated mice returned to pre-treatment levels and the mice displayed decreased disease parameters including smaller and fewer colonic lesions as well as smaller reductions of colon length (17).

Obefazimod also decreased macrophages recruitment into the mouse colon tissue during DSS acute colitis (17).

1.4 Non-Clinical Background Information

The toxicity of obefazimod and ABX464-N-Glu was studied in a range of rodent and non-rodent species (rats, rabbits, dogs, cynomolgus and marmoset monkeys, and minipigs) with treatment durations ranging from 2 weeks to 6 or 9 months. These studies demonstrated that obefazimod and ABX464-N-Glu are overall well tolerated. [redacted] were the major clinical signs, and the main target organs of obefazimod toxicity were the [redacted]

Obefazimod had no significant adverse effects on the nervous and respiratory systems, or on cardiovascular function. Obefazimod and ABX464-N-Glu were found to be non-genotoxic. [redacted]

Regarding the other observations made from the nonclinical toxicology program, refer to the current version of the Investigator's Brochure.

1.5 Ongoing and Completed Clinical Trials with Obefazimod

Assessment of obefazimod in humans is ongoing:

- Completed clinical studies: in healthy volunteers (ABX464-001, ABX464-002, ABX464-901, ABX464-902, ABX464-903, ABX464-905 [drug product formulation study], and ABX464-921 [bioequivalence study in Japanese Healthy Volunteers]), in subjects with UC (ABX464-101, ABX464-102 and ABX464-103) in subjects with rheumatoid arthritis (ABX464-301 and ABX464-302), in HIV-infected subjects (ABX464-003, ABX464-004, and ABX464-005) and in COVID-19 infected subjects (ABX464-401).

- Ongoing and planned studies in UC (ABX464-104*, ABX464-105, ABX464-106, ABX464-107 and ABX464-108), in Crohn's disease (ABX464-202), in subjects with hepatic impairment (ABX464-908) and in healthy volunteers (ABX464-906 and ABX464-910 [redacted]

  **The clinical phase of study ABX464-104 has been completed (last subject last visit has occurred) however the study is considered ongoing until the final CSR is available.*

As of 30 November 2023, 1082 subjects have received obefazimod, according to various administration schedules, in all completed and ongoing open-label clinical studies across all indications, including 248 subjects for longer than 6 months and 226 subjects for longer than one year. Additionally, 146 subjects included in the ABTECT program (ABX464-105, ABX464-106 and ABX464-107) have received the blinded IMP (obefazimod or placebo).

Clinical Pharmacology

Obefazimod was rapidly absorbed and metabolized [redacted] within 1 to 4 hours of treatment, regardless of dose level. After repeated administration of obefazimod, an initial decrease in obefazimod plasma area under the curve was observed until steady state was reached after 4 weeks of treatment. [redacted] Food intake prior to administration significantly increased obefazimod exposure, by at least 3- to 4-fold.

Clinical Efficacy

Obefazimod studies in UC with database locked are:

- Phase 2a program with an 8-week induction study (ABX464-101) and a 4-year maintenance study (ABX464-102)
- Phase 2b program including the 16-week induction study (ABX464-103) and an open-label extension study (ABX464-104)

ABX464-103 was a randomized, double-blind, placebo-controlled phase 2b induction study and was conducted at 95 study sites in 15 European countries, Canada, and the USA, investigating three oral obefazimod treatment groups (25, 50 and 100 mg QD) and one placebo group. A total of 254 subjects with moderate to severely active UC were enrolled into the trial. Of these subjects, 50% had previous inadequate response, loss of response, or intolerance to TNF-α inhibitors, vedolizumab, other biologics and/or JAK inhibitors treatments, while the other 50% were refractory to conventional treatments. Endoscopies were read centrally and blinded by independent reviewers. Electronic subject diaries were used to optimize validity and reliability of the collection of stool frequency, rectal bleedings, and other patient-reported outcomes (PROs). Gender, clinical, biological, and endoscopic parameters were well distributed across placebo and treatment groups at enrolment. The primary endpoint, i.e., the reduction of the modified Mayo Score (MMS) from baseline after 8 weeks of treatment, was statistically significant for all active treatment groups (Table 1). ABX464-103 study was completed in April 2021.

Table 1: Primary and Secondary Efficacy Endpoints in Study ABX464-103

Week 8 Results		Placebo N=64	25mg N=61	50mg N=63	100mg N=64
Primary Endpoint					
Modified Mayo Score Mean change from baseline	All patients	N=60	N=59	N=54	N=58
		-1.9	-3.1 *	-3.2 *	-2.9 *
	Bio exposed	N=27	N=28	N=23	N=29
		-1.0	-2.8 *	-2.9 *	-2.8 *
	p-values of <0.01 versus placebo for all dose groups (ANCOVA)				
Key Secondary Endpoints (not powered for statistical significance)					
Endoscopic Improvement [a, d]	All patients	n/N=8/60	n/N=20/59	n/N=21/54	n/N=24/58
		13.3%	33.9% *	38.9% *	41.4% *
	Bio exposed	n/N=1/27	n/N=8/28	n/N=7/23	n/N=8/29
		3.7%	28.6% *	30.4% *	27.6% *
	p-values of <0.05 versus placebo for all dose groups using a likelihood ratio Chi-squared test				
Clinical Remission [b, d]	All patients	n/N=8/60	n/N=17/59	n/N=11/54	n/N=16/58
		13.3%	28.8% *	20.4%	27.6%
	Bio exposed	n/N=1/27	n/N=6/28	n/N=2/23	n/N=6/29
		3.7%	21.4% *	8.7%	20.7% *
	p-values of <0.05 versus placebo using a likelihood ratio Chi-squared test but not according to the predefined Mantel-Haenszel Chi Square test (p<0.1)				
Clinical Response [c, d]	All patients	n/N=23/60	n/N=40/59	n/N=38/54	n/N=35/58
		38.3%	67.8% *	70.4% *	60.3% *
	Bio exposed	n/N=5/27	n/N=17/28	n/N=13/23	n/N=15/29
		18.5%	60.7% *	56.5% *	51.7% *
	p-values of <0.05 versus placebo for all dose groups using a likelihood ratio Chi-squared test				

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

Obefazimod was shown to be effective in all subjects and, importantly, also in subjects with inadequate response, loss of response, or intolerance to biologics and/or JAK inhibitors. These efficacy results warranted the continuation of the development of obefazimod in UC.

ABX464-104 was a phase 2b, open label, efficacy, and safety study of obefazimod as maintenance therapy in subjects with moderate to severe UC. Most subjects (97.7%) who completed the phase 2b induction study (ABX464-103), irrespective of treatments or treatment outcome during the induction study, enrolled into the open-label maintenance study (ABX464-104) to evaluate the long-term safety and efficacy profile of obefazimod for up to 2 years.

Of the 222 subjects who completed the 16-week phase 2b induction trial, ABX464-103, 217 patients (98%) enrolled in the subsequent open-label maintenance trial, ABX464-104, to evaluate the long-term safety and efficacy profile of obefazimod for up to two years. At Week 48, of those 217 patients who received 50 mg QD oral dosing with obefazimod, 178 patients (82%) had clinical response, 119 patients (55%) were in clinical remission, 133 patients (61%) had endoscopic improvement, and 72 patients (33%) had endoscopic remission.

Moreover, at Week 48, 38 patients were in sustained clinical remission and 107 patients showed sustained clinical response. A total of 70 patients exhibited de novo clinical response and 81 patients exhibited de novo clinical remission. Among the 98 bio-refractory patients, 66 patients (67%) had a clinical response, 38 patients (39%) were in clinical remission, 46 patients (47%) had an endoscopy improvement, and 20 patients (20%) had an endoscopy remission at Week 96. These results demonstrate the long-term clinical

response of obefazimod in patients who were refractory to conventional treatments, as well as patients who were previously exposed to biologics and/or JAK inhibitors treatment.

At Week 96, of the 49 patients who were in clinical remission at the end of the induction phase, 33 patients (67%) remained in clinical remission. Of the 168 patients who were not in clinical remission at the end of the induction phase, 81 patients (48%) exhibited de novo clinical remission. Furthermore, the clinical remission rate for patients who did not show at least a clinical response at the end of the 8-week induction phase was 43% (40 patients). Of the patients included in the maintenance trial, 164 patients (75%) completed two years of QD oral dosing with 50 mg obefazimod. Thirty patients dropped out during the first year of treatment. Six patients did not qualify for the second year due to non-response after the first year of treatment, and 17 patients dropped out during the second year. These subjects were all considered treatment failures in the intent-to-treat analysis. During the phase 2b induction study and open label maintenance study, the clinical safety and tolerability profile observed was consistent with previous findings and no new clinical adverse safety signals were identified.

Clinical Safety

Overall obefazimod is well tolerated. The most frequently reported adverse events (AEs) were headache, nausea, vomiting, abdominal pain, back pain, and diarrhea which were mostly of mild to moderate intensity, generally occurring shortly after treatment onset and transient in nature.

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

[redacted]

obefazimod, no signs of hepatotoxicity have been observed in any of the subjects treated with obefazimod in completed or ongoing clinical studies. The Sponsor and its clinical experts consider that subjects treated with obefazimod are not at increased risk of developing drug-induced hepatotoxicity.

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

1.6 Study Rationale

This study is part of a phase 3 clinical development program comprising two similar 8-week induction studies (ABX464-105 and ABX464-106), followed by a maintenance study (ABX464-107) to confirm the efficacy and safety of obefazimod in the short and long-term treatment of moderate to severely active UC in adults and adolescents from 16 to 18 years of age. The maintenance study, which will be proposed to all eligible and willing subjects from both induction studies, consists of a 44-week maintenance pivotal study, followed by an optional long-term extension (LTE) that will last for an additional 4 years, or until the commercialization of obefazimod, whichever occurs first.

1.6.1 Dose selection and treatment duration

The present ABX464-105 study is a phase 3 study designed to characterize the efficacy and safety of 2 doses of obefazimod, 25 mg and 50 mg, as induction therapy in subjects with moderately to severely active UC. Obefazimod for the treatment of UC has been shown to induce and sustain clinical remission in subjects with moderate to severe UC in phase 2a and phase 2b induction and maintenance studies (ABX464-101, ABX464-102, ABX464-103, ABX464-104).

The 50 mg dose represents the most studied dose regimen across obefazimod clinical development with 848 subjects dosed at 50 mg QD including 232 subjects dosed for longer than 6 months and 209 subjects for more than a year. Focusing on UC studies, 259 subjects have been dosed with 50 mg QD corresponding to 4903 subject-months. Clinical experience accumulated at this dose level demonstrates that 50 mg provides a high level of efficacy during induction and maintenance, together with a favorable short and long-term safety profile. The ABX464-103 phase 2b UC study has demonstrated that the 25 mg dose was also efficacious for induction with a safety profile comparable to placebo (except transient headaches generally reported during the first several days of treatment). The 100 mg dose showed similar efficacy to the 25 and 50 mg doses but with a higher incidence of most frequently reported TEAEs and was not selected for this

program. Therefore, the choice to use both 25 and 50 mg obefazimod as an induction treatment dose is deemed relevant.

Treatment duration was different in both phase 2a and 2b studies: It was 8 weeks in ABX464-101 (phase 2a) and 16 weeks in ABX464-103 (phase 2b). Interestingly, the primary endpoint as defined in ABX464-103, i.e., the reduction of the modified Mayo Score (MMS) from baseline after 8 weeks of treatment showed reductions that were statistically significant relative to placebo for all active treatment groups (Table 1) After 16 weeks of treatment there were a limited number of patients who achieved a clinical response that was not observed at Week 8. Therefore, it is reasonable to define 8 weeks as the treatment duration for the induction study.

To evaluate the efficacy of obefazimod for UC, this study includes a placebo-controlled group during the 8-week induction period. The purpose of the placebo comparison is to determine the treatment effects that are not due to obefazimod itself (i.e., placebo effect). Factors accounting for the placebo effect which may lead to improvement in UC symptoms include increased attention from healthcare providers in the context of a clinical study, aspirations of receiving the active treatment, the expectation of a treatment's benefit because of its novelty, or spontaneous improvement in the UC symptoms as part of the disease course (ie, flares and quiescent states). At study entry, subjects randomized to any treatment group may continue certain background therapy for UC (e.g., 5-aminosalicylic acid [5-ASA] compounds and/or oral CS); therefore, even subjects randomized to the placebo treatment during the treatment period will have concomitant therapies that may be partially effective at controlling UC symptoms.

2 Study Objectives and Endpoints

2.1 Study-specific Definitions

For the purpose of the study, the following definitions will be applied:

Baseline is defined as the last non-missing assessment performed prior to first dose of study drug, unless stated otherwise.

Modified Mayo Score (MMS) is defined as the sum of 3 component scores: Rectal bleeding subscore (RBS), Stool Frequency subscore (SFS) and Mayo Endoscopic subscore (MES).

Partial Modified Mayo Score (pMMS) is defined as combination of RBS and SFS.

Total Mayo Score (TMS) is defined as the sum of 4 component scores: RBS, SFS, MES and Physician's Global Assessment subscore (PGA).

Clinical remission is defined as SFS = 0 or 1, and RBS = 0 and MES = 0 or 1 (MES of 1 modified to exclude friability).

Clinical response is defined as a reduction from baseline in MMS ≥ 2 points and a relative reduction from baseline in MMS ≥ 30%, and a reduction from baseline in RBS ≥ 1 point and/or RBS = 0 or 1.

Partial Clinical response per pMMS is defined as a reduction from baseline in pMMS ≥ 1 points and a relative reduction from baseline in pMMS ≥ 30%, and a reduction from baseline in RBS ≥ 1 point and/or RBS = 0 or 1.

Symptomatic remission is defined as SFS = 0 or 1 and RBS = 0.

Endoscopic improvement is defined as MES = 0 or 1 (MES of 1 modified to exclude friability).

Endoscopic remission is defined as MES = 0.

Histologic improvement is defined as Geboes Index score ≤ 3.1.

Histologic remission is defined as Geboes Index score < 2.0 (no neutrophils or eosinophils in lamina propria or in epithelium, no erosion, no ulceration).

Histologic-endoscopic mucosal improvement (HEMI) is defined as endoscopic improvement associated with histologic improvement per Geboes scoring.

Histologic-endoscopic mucosal remission (HEMR) is defined as endoscopic remission associated with histologic remission per Geboes scoring.

Conventional therapies include oral 5-ASA and sulfasalazine, oral or injectable corticosteroids (CS) and immunosuppressants (IS).

Advanced therapies include biologics and biosimilars (anti-TNF [e.g., adalimumab, infliximab, golimumab], α4β7 anti-integrins [e.g., vedolizumab], anti-IL12/23 [e.g., ustekinumab, mirikizumab]), S1P receptor modulators (e.g., ozanimod, etrasimod), and JAK inhibitors (e.g., tofacitinib, filgotinib, upadacitinib) and potential new approved drugs.

Nocturnal Bowel Movement (NBM) is defined as one or more sleep interruptions due to a bowel movement.

Bowel Urgency (BU) is defined as a sudden, almost uncontrollable need to go to the toilet due to bowel movement.

Extra Intestinal Manifestations (EIM) are defined as ocular manifestations (uveitis, scleritis, episcleritis), rheumatological manifestations (axial spondyloarthritis, peripheral spondyloarthritis, arthralgia) or dermatological manifestations (psoriasis, pyoderma gangrenosum, erythema nodosum).

Inflammatory Bowel Disease (IBDQ) response is defined as an increase of IBDQ total score ≥ 16 from Baseline.

IBDQ remission is defined as an IBDQ total score ≥ 170.

2.2 Study Objectives and Endpoints

Primary and secondary endpoints will be adequately adjusted for multiplicity to protect the type-I error rate using a fallback method. Details can be found in Section 9.3.1, which follows the US Food and Drug Administration (FDA) guidance and Section 9.3.2, which follows the European Medicines Agency (EMA) guidance.

2.2.1 Primary Objective and Endpoint

The primary/co-primary and key secondary efficacy endpoints will be analyzed separately for FDA and National Regulatory Authorities other than EMA.

- For the FDA and National Regulatory Authorities other than EMA purposes, the primary efficacy objective is to compare the efficacy of obefazimod versus placebo on clinical remission defined as:
  - *Proportion of subjects in clinical remission at Week 8.*
- For the EMA purposes, the primary efficacy objective is to compare the efficacy of obefazimod versus placebo on endoscopic improvement and symptomatic remission. The co-primary endpoints are defined as:
  - *Proportion of subjects who achieve endoscopic improvement at Week 8*
  - *Proportion of subjects with symptomatic remission at Week 8.*

2.2.2 Key Secondary Efficacy Objectives and Endpoints

For the FDA and National Regulatory Authorities other than EMA, the key secondary efficacy objectives and endpoints are:

- To compare the efficacy of obefazimod versus placebo on endoscopic improvement.
  - *Proportion of subjects who achieve endoscopic improvement at Week 8.*
- To compare the efficacy of obefazimod versus placebo on clinical response.
  - *Proportion of subjects with clinical response at Week 8.*
- To compare the efficacy of obefazimod versus placebo on HEMI.
  - *Proportion of subjects with HEMI per Geboes scoring at Week 8.*

For the EMA, the key secondary efficacy objectives and endpoints are:

- To compare the efficacy of obefazimod versus placebo on clinical remission.
  - *Proportion of subjects who achieve clinical remission at Week 8.*
- To compare the efficacy of obefazimod versus placebo on clinical response
  - *Proportion of subjects with clinical response at Week 8.*
- To compare the efficacy of obefazimod versus placebo on HEMI.
  - *Proportion of subjects with HEMI per Geboes scoring at Week 8.*

2.2.3 Other Secondary Objectives and Endpoints

Other secondary efficacy objectives and endpoints are:

- To compare the efficacy of obefazimod versus placebo on MMS.
  - *Change from baseline in MMS at Week 8.*
- To compare the efficacy of obefazimod versus placebo on pMMS.
  - *Change from baseline in pMMS by visit.*
- To compare the efficacy of obefazimod versus placebo on partial clinical response.

- *Proportion of subjects with partial clinical response by visit.*

- To compare the efficacy of obefazimod versus placebo on RBS.
  - *Proportion of subjects with RBS = 0 by visit.*
- To compare the efficacy of obefazimod versus placebo on SFS.
  - *Proportion of subjects with SFS = 0 or 1 by visit.*
- To compare the efficacy of obefazimod versus placebo on BU.
  - *Proportion of subjects with BU = 0 by visit in the subpopulation of subjects with BU at baseline.*
- To compare the efficacy of obefazimod versus placebo on Fecal Calprotectin (FC).
  - *Change from baseline in FC by visit.*
  - *Proportion of subjects with FC below 150µg/g by visit.*
- To compare the efficacy of obefazimod versus placebo on Fatigue Numeric Rating Scales (NRS).
  - *Change from baseline in the fatigue NRS by visit*.
- To compare the efficacy of obefazimod versus placebo on FACIT-Fatigue questionnaire.
  - *Change from baseline in the FACIT-Fatigue at Week 8*.
- To compare the efficacy of obefazimod versus placebo on histologic improvement.
  - *Proportion of subjects who achieve histologic improvement per Geboes scoring at Week 8.*
- To compare the efficacy of obefazimod versus placebo on endoscopic remission.
  - *Proportion of subjects who achieve endoscopic remission at Week 8.*
- To compare the efficacy of obefazimod versus placebo on HEMR.
  - *Proportion of subjects with HEMR per Geboes scoring at Week 8.*
- To compare the efficacy of obefazimod versus placebo on histologic remission.
  - *Proportion of subjects who achieve histologic remission per Geboes scoring at Week 8.*
- To compare the efficacy of obefazimod versus placebo on IBDQ.
  - *Change from Baseline in IBDQ total score and domain subscores at Week 8.*
  - *Proportion of subjects with IBDQ response at Week 8.*
- To compare the efficacy of obefazimod versus placebo on NBM.
  - *Proportion of subjects with no more NBM by visit in the sub-population of subjects with NBM at baseline.*
- To compare the efficacy of obefazimod versus placebo on EIM.
  - *Proportion of subjects with no EIM at Week 8 in the subpopulation of subjects having EIM at baseline.*
- To compare the efficacy of obefazimod versus placebo on symptomatic remission.
  - *Proportion of subjects with symptomatic remission by visit.*
- To compare the efficacy of obefazimod versus placebo on EQ-5D-5L.
  - *Change from baseline in EQ-5D-5L score by visit.*
- To compare the efficacy of obefazimod versus placebo on hsCRP.

- *Change from baseline in hsCRP by visit.*

- To compare the efficacy of obefazimod versus placebo in WPAI.
  - *Change from baseline in WPAI:UC score at Week 8.*
- To compare the efficacy of obefazimod versus placebo on any UC-related Emergency Room (ER) visits, hospitalizations and/or surgery.
  - *Proportion of subjects with UC-related visits to ER, hospitalizations and/or surgery.*
- To compare the effect of obefazimod versus placebo on miR-124 expression in tissue and in blood.
  - *Change from baseline in miR-124 expression in rectal/sigmoidal biopsies at Week 8 and in blood by visit.*
- To compare the effect of obefazimod versus placebo on proinflammatory cytokine plasma concentrations.
  - *Change from baseline in proinflammatory cytokine plasma concentrations by visit.*
- To assess the concentration of obefazimod [redacted] after oral administration.
  - *Plasma concentrations of obefazimod [redacted] at baseline, Week 4 and Week 8 (at specified time points depending on the group allocated via IWRS).*

2.2.4 Safety Objective and Endpoints

Safety objectives and endpoints are:

- To evaluate the safety profile of obefazimod versus placebo during induction:
  - *Incidence of all treatment-emergent adverse events (TEAEs), causally-related TEAEs, all serious TEAEs and causally-related serious TEAEs classified by severity.*
  - *Incidence of TEAEs leading to investigational medicinal product (IMP) discontinuation and study discontinuation.*
  - *Incidence of treatment-emergent AESIs.*
  - *Incidence of clinically significant laboratory abnormalities.*
  - *Incidence of clinically significant abnormalities regarding vital signs and electrocardiograms (ECGs).*

2.2.5 [redacted]

- [redacted]

For this purpose, several parameters will be assessed as stated in Section 5.3.5 and Section 9.7.

See Section 9.3 for details on primary estimand attributes.

3 Investigational Plan

3.1 Study Design and Methodology

This induction study is a multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of obefazimod given at 25 or 50 mg QD in inducing clinical remission in subjects with moderately to severely active UC who have inadequate response (lack of response, loss of response, intolerance) to either conventional therapies and/or advanced therapies.

As shown in

Figure 3, this study consists of a screening period of up to 4 weeks, an 8-week induction period followed by 4 week follow up period. Subjects who complete the 8-week induction will be given the opportunity to take part in the maintenance study (ABX464-107) either:

- In the randomized double-blind placebo-controlled study part (Part 1; placebo, obefazimod 25 mg, obefazimod 50 mg) for clinical responders at Week 8.
- In the double-blind, multi-arm study part (Part 2; obefazimod 25 mg or obefazimod 50 mg) for non-clinical responders at Week 8.

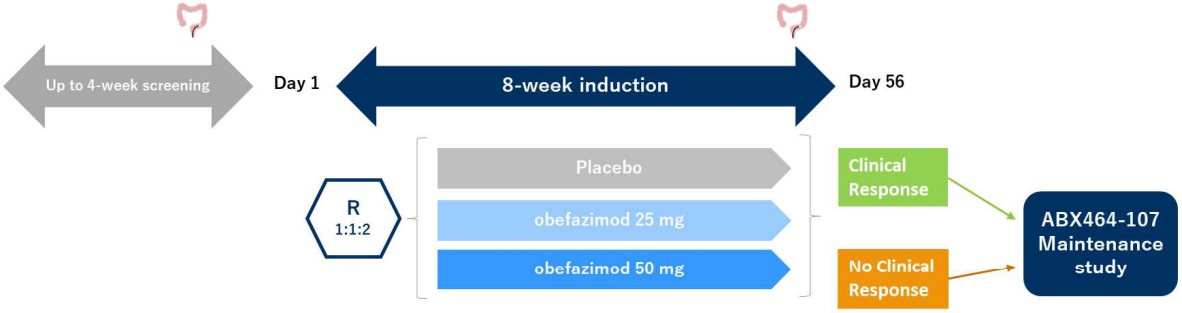
Parts 1 and 2 will last up to 44 weeks. Eligible subjects will then be offered the option to continue in the LTE phase of this study for up to 4 additional years or until the commercialization of obefazimod, whichever occurs first.

Approximately 612 subjects will be randomized in this induction study.

On Day 1, eligible subjects will be randomized and allocated into three treatment arms according to ratio 1:1:2 as follows:

- Placebo: 153 subjects
- Obefazimod 25 mg QD: 153 subjects
- Obefazimod 50 mg QD: 306 subjects

Figure 3: Study Design



Randomization will be stratified according to the following:

- Subjects with inadequate response to advanced therapies (AT-IR subjects [lack of response, loss of response, or intolerance to advanced therapies]) (Yes/No)
- Subjects with concomitant oral CS at baseline (Yes/No)

Approximately [redacted] of the randomized subjects should have inadequate response to advanced therapies. In addition, [redacted].

Previous discontinuation of an advance therapy for any reason other than inadequate response, e.g., pregnancy, economic reasons or termination of a clinical trial, will not be considered as AT-IR. In addition to the on-site visit on Day 1 (randomization day), onwards, subjects will be seen at the investigational site at Week 4 and Week 8 according to the study schedule of assessments.

Subjects will also be provided with the direct phone number of the investigational site (i.e., patient card) in order to call the investigator in case UC symptoms are worsening between on-site visits.

Subjects will be evaluated for safety and efficacy throughout the induction study.

During the screening period, a full colonoscopy will be performed for all subjects unless one has been performed within the last 3 months before screening. The following information must be noted in the local endoscopic report: UC extension, lack of colonic cancer, lack of low grade or high-grade dysplasia adenomatous polyps (fully removed or not). At Week 8, only a flexible sigmoidoscopy is required. At screening and Week 8, during both endoscopic procedures, biopsies will be performed at the most severely affected area. Endoscopies will be centrally read. Sigmoidoscopy might be substituted by a full colonoscopy if requested by national medical practices and/or guidelines. Biopsies will be centrally analyzed.

e-Diaries will be used to collect stool frequency, rectal bleedings, NBM, BU and fatigue NRS on a daily basis, as well as whether subjects took the study treatment and the intake time.

PK samples will be collected[redacted]. Subjects will be allocated into two different groups via IWRS. At each time point collection (D1, D28, D56) samples will be taken as follows:

- for group 1: pre-dose, 0.5, 1.5, 3 h (and 6 h and/or 10 h if possible) post-dose
- for group 2: pre-dose, 1, 2, 4 h (and 8 h and/or 12 h if possible) post-dose

A time window of ± 10 minutes is allowed for each time point collection.

[redacted]

At Week 8, subjects who meet eligibility criteria [redacted] to either take part in the maintenance (ABX464-107) study or to end their participation in the present induction study by completing the end of study visit (4 weeks after the last study drug intake). However, subjects who are eligible for the ABX464-107 study should be encouraged to enter it.

3.2 Committees

3.2.1 Independent Data Monitoring Committee (IDMC)

An IDMC, with required medical expertise and experience in biostatistics, and independent from the sponsor and the conduct of the trial, will be set up specifically to guarantee effective protection of subjects, ensure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.

The IDMC will meet quarterly after the first subject has been randomized until the last subject has completed the study.

The IDMC will oversee the adequate balance of baseline characteristics (i.e., gender, disease duration, prior and concomitant UC medication) among the treatment groups and will review safety and efficacy data.

Furthermore, the IDMC will also review all potential causally related SAEs within 7 days of the initial notification by an investigating site.

The IDMC may also recommend the initiation of a separated “Feeder” study (ABTECT Feeder) should the number of subjects with a clinical response at Week 8 who are eligible for randomization into the maintenance study (ABX464-107) be lower than the number of subjects planned in the maintenance study. The ABTECT Feeder study, if required, should start once subject’s enrollment of the two pivotal induction studies is completed. All subjects will be dosed with obefazimod 25 mg QD. Study details will be similar to the induction studies other than the open-label dose.

The IDMC has a consultative role. It will provide a recommendation to the Sponsor, who will decide whether to follow the recommendation. The IDMC may recommend the early termination of the trial at any time if an unacceptable toxicity occurs.

An IDMC charter will be available upon submission of the trial (initial protocol) to the respective Regulatory Authorities.

3.2.2 Study Steering Committee (SSC)

The role of the Study Steering Committee (SSC) is to advise the Sponsor on the design and execution of the study to ensure scientific validity and clinical relevance of the study protocol and results. During the study, discussions between the Sponsor and SSC will focus on adherence to the protocol, subject safety, and consideration of new information of relevance to the indication pursued. The Sponsor will organize meetings either by teleconference or face-to-face with the SSC approximately every 4-6 months during the conduct of the study. In addition, the SSC may periodically be called upon to provide advice, through its co-chairs or more broadly, to the coordinating investigators and the Sponsor on all appropriate aspects of the study. The SSC will continue in the capacity described at least until the results of the study have been published in a scientific journal and potentially longer, as requested by the Sponsor.

3.2.3 [redacted]

[redacted]

3.3 Duration of Study Participation

The induction study ABX464-105 includes the following phases:

- Up to 4 weeks of screening.
- 8 weeks of induction.
- 4 weeks of safety follow-up (only for subjects not willing, or not eligible, to enter the maintenance study).

The total study duration is 12 weeks for eligible subjects willing to join the maintenance study (ABX464-107) after their participation in study ABX464-105.

The total study duration for subjects not willing to join the maintenance study (ABX464-107) or not eligible for it, is 16 weeks.

4 Study Population

4.1 Study Population

The current study protocol aims to recruit the same population profile as for the phase 2 studies, ABX464-101 and ABX464-103 studies, i.e., subjects with moderately to severely active UC who have inadequate response (lack of response, loss of response, or intolerance) to either conventional therapies and/or advanced therapies.

Pharmacokinetic (PK) modeling and simulations show that the PK profile of obefazimod is expected to be the same in subjects aged 16 to 18 years old compared with older subjects. These data provide the rationale to recruit younger subjects starting from the age of 16 years old.

In this study, subjects aged from 16 years will be recruited. However, no adolescents will be recruited in the EU/EEA and Ukraine, or from any other country unless authorized by the respective Regulatory Authorities and IEC-IRB.

4.2 Number of Subjects/Centers

Approximately 612 subjects are expected to be enrolled in this study in up to 350 investigational sites located worldwide.

4.3 Eligibility Criteria

4.3.1 Inclusion Criteria

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

1. Male or female (at birth) at least 16 years old except in EU/EEA and Ukraine, where subjects must be at least 18 years old at the time of eligibility assessment. Where enrolment of adolescent subjects is allowed, adolescent subjects must weigh ≥ 40 kg and meet the definition of Tanner Stage 5 at screening.
2. Subjects must understand, sign and date the written voluntary informed consent form at the visit prior to any protocol-specific procedures. For under-aged subjects, national requirements regarding consent should also be met.
3. Documented diagnosis of UC, confirmed by endoscopy and histology. Should endoscopy/histology results not be available at screening, results from endoscopy and biopsies taken at screening may be used.
4. Active disease defined by modified Mayo score (MMS) ≥ 5 with rectal bleeding subscore (RBS) ≥ 1 and endoscopy subscore (MES) of 2 or 3 (confirmed by central reader).
5. Subjects with documented inadequate response (defined as lack of response, loss of response and/or intolerance) to at least one of the following treatments: corticosteroids (CS), immunosuppressants (IS), biologic or biosimilar therapies, S1P receptor modulators, JAK inhibitors and/or new drugs approved during the study (note: inadequate response to only 5-ASA or sulfasalazine is not accepted).
    a. Inadequate response to CS is defined as:
        i. CS resistance (i.e., signs and symptoms of persistently active disease despite current or prior course of equivalent prednisone/prednisolone ≥ 40 mg/d for at least 2 weeks, or to budesonide ≥ 9 mg/d for at least 2 weeks, or to beclomethasone ≥ 5 mg/d for at least 2 weeks);
        ii. CS dependence:
            1. failure to taper to ≤10 mg of equivalent prednisone/prednisolone, < 9 mg/d of budesonide or < 5 mg of beclomethasone;
            2. relapse occurring within 3 months after stopping CS;
            3. exposure to corticosteroids > 4 months;
        iii. Intolerance to CS including (but not limited to) Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection.
    b. Inadequate response to IS is defined as:

i. Signs and symptoms of persistently active disease despite azathioprine treatment ≥ 1.5 mg/kg/day for at least 8 weeks, or mercaptopurine ≥ 0.5 mg/kg/day for at least 8 weeks, or methotrexate ≥ 12.5 mg/week for at least 8 weeks;

ii. Intolerance to IS including (but not limited to) nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, infection.

c. Inadequate response to biologics or biosimilars (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, mirikizumab) is defined as:

i. Lack of response to an induction course;

ii. Loss of response or recurrence of symptoms during maintenance course following primary response after induction course (discontinuation despite clinical benefit does not qualify);

iii. Intolerance to biologics or biosimilars including (but not limited to) infusion-related reaction, serious opportunistic infection, malignancies.

d. Inadequate response to JAK inhibitors (tofacitinib, filgotinib, upadacitinib) is defined as:

i. Lack of response to an induction course;

ii. Loss of response or recurrence of symptoms during maintenance course following primary response after induction course (discontinuation despite clinical benefit does not qualify);

iii. Intolerance to JAK inhibitor treatment including (but not limited to) increase of serious infection, malignancies, deep venous thrombosis (DVT), or major adverse cardiac event (MACE).

e. Inadequate response to S1P receptor modulators (ozanimod, etrasimod) is defined as:

i. Lack of response to an induction course;

ii. Loss of response or recurrence of symptoms during maintenance course following primary response after induction course (discontinuation despite clinical benefit does not qualify);

iii. Intolerance to S1P receptor modulators including (but not limited to) serious infections, liver enzyme, cardiac abnormalities, lymphopenia.

f. Lack of response, loss of response, or intolerance to any new drug approved for moderate to severe active UC during the course of the study.

6. Women of childbearing potential (WOCBP) subjects and male subjects with WOCBP partner must agree to comply with contraception requirements as described in Section 4.5 of this protocol.
7. Subjects able and willing to comply with study visits and procedures as per protocol.
8. Subjects should be affiliated to a health insurance policy whenever required by a participating country or state.

4.3.2 Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria will be excluded from the study:

1. Subjects with UC limited to an isolated proctitis (< 15cm from anal verge) determined by endoscopy central reading.
2. Subjects with primary sclerosing cholangitis or autoimmune hepatitis.
3. Subjects who had inadequate response to 5-ASA or sulfasalazine therapy only.
4. Subjects with CD, presence or history of fistula, indeterminate colitis, infectious/ischemic colitis or microscopic colitis (lymphocytic and collagenous colitis).
5. History or current evidence of toxic megacolon, fulminant colitis, bowel perforation.

6. History of colonic cancer or colonic low grade or high grade dysplasia adenomatous polyps, and/or at the screening endoscopy, evidence of colonic cancer or evidence of low grade or high grade dysplasia adenomatous polyps (fully removed or not).
7. Recent or planned bowel surgery or history of proctocolectomy or partial colectomy or current stoma.
8. Subjects on antidiarrheals including those working on motility (e.g., loperamide, diphenoxylate with atropine, etc.).
9. Subjects on probiotics (e.g., Culturelle® [Lactobacillus GG, i-Health, Inc.], *Saccharomyces boulardii*).
10. Subjects who do not meet the washout period requirements prior to the screening endoscopy as described in the prohibited medication section (Section 4.4.2) of the study protocol.
11. Subjects with the following hematological and biochemical laboratory parameters obtained during the screening period:
    a. Hemoglobin ≤ 8.0 g dL^{-1}
    b. Absolute neutrophil count < 750 mm^{-3}
    c. Platelets < 100,000 mm^{-3}
    d. Creatinine clearance < 60 $mL.min^{-1}$ (Cockroft-Gault formula)
    e. Total serum bilirubin > 1.5 x upper limit of normal (ULN) (except if related to pre-existing and documented Gilbert syndrome)
    f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x ULN
12. Subjects with the following conditions (infection):
    a. Subjects with chronic or recurrent grade 3 or grade 4 infection within the last 2 months prior to screening or a history of opportunistic infection while not on immunosuppressive therapy.
    b. Herpes zoster reactivation within the last 2 months prior to screening.
    c. Subjects with active infection at screening or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 1 month of screening or during screening. Fungal infection of nail beds is allowed.
    d. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or positive test for Clostridium difficile toxins at screening. If C. difficile is positive, subject may be treated and retested ≥ 2 weeks after completing treatment.
    e. Subjects with HIV infection.
    f. Subjects having acute or chronic hepatitis B infection at screening (positive for hepatitis B surface antigen [HbsAg], or negative for HbsAg and positive for anti-hepatitis B core antibody in conjunction with detectable HBV DNA, or detectable HBV DNA).
    g. Subjects having acute or chronic hepatitis C infection at screening as defined by positive for hepatitis C antibody and positive HCV RNA (subjects successfully treated and without recurrence ≥ 1 year with no detectable HCV RNA [assessed centrally] are eligible).
    h. Active tuberculosis (TB) or untreated latent TB are ruled out. For subjects with positive or intermediate QuantiFERON test see Section 5.3.8.1 of the current study protocol.
13. Subjects with an uncontrolled ischemic heart disease and/or a history of congestive heart failure with New York Heart Association (NYHA) class 3 or 4 symptoms.
14. Subjects with a family or personal history of congenital or acquired long QT syndrome, or subjects with a marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval [Fridericia correction] >450 milliseconds for male and > 460 milliseconds for female).
15. Subjects with a history of torsade de pointe (TdP).

16. Acute or chronic clinically relevant pulmonary, hepatic, or renal functional abnormality, encephalopathy, neuropathy, or unstable central nervous system pathology such as seizure disorder, or any other clinically significant medical problems as determined by physical examination and/or laboratory screening tests and/or medical history (note: treated autoimmune hypothyroidism and autoimmune diabetes are allowed).
17. [redacted]
18. History or active [redacted]
19. Serious illness requiring hospitalization within 4 weeks prior to screening (except UC flare).
20. Subjects previously treated with obefazimod.
21. Subjects with a known hypersensitivity to the active substance or to any of the excipients.
22. WOCBP subject who is pregnant or breast-feeding at screening, or intends to become pregnant during the study, or male subject with WOCBP partner who intends to be pregnant during the study.
23. Illicit drug or alcohol abuse or dependence.
24. [redacted]
25. Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer, and during the study.
26. Subjects committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
27. Any condition, which in the opinion of the investigator, could compromise the subject's safety or adherence to the study protocol.

4.4 Allowed and Prohibited Concomitant Medications

All previous UC medications on which failure of treatment has occurred will be recorded into the eCRF without time limitation for advanced therapies and over the past 5 years for conventional treatments. Previous and current medications will be reviewed to check the use of potentially prohibited medication and ensure appropriate washout period is respected. Any change in concomitant medication will be duly checked at each study visit or by phone by site personnel. All concomitant medications will be recorded into the eCRF.

4.4.1 Allowed Concomitant Treatment

For the treatment of UC (provided stable dose for at least 2 weeks prior to the screening endoscopy and during the whole induction study) the following medications are allowed upon entry into the study:

- CS: prednisone or prednisone equivalent ≤ 15 mg/day; beclomethasone dipropionate (≤ 5 mg/day) or budesonide MMX (≤ 9 mg/day).
- Oral 5-ASA.

4.4.2 Prohibited Medications and Procedures

The following medications and procedures are prohibited from enrollment, throughout the entire study, until study discontinuation. For some of them used prior to subjects' enrollment a strict washout period may apply. Sites are allowed to assay drug levels during the study period to shorten the washout periods.

Prohibited Medications:

- Initiation of any oral, injectable, or rectal CS, or oral and rectal aminosalicylates and other enemas/suppositories (other than required for endoscopy) is prohibited starting 2 weeks prior to the Screening endoscopy.
- Cyclosporine, tacrolimus, mycophenolate mofetil, or thalidomide must be stopped at least 4 weeks prior to Screening endoscopy.

- Azathioprine or 6-mercaptopurine or methotrexate must be stopped at least 2 weeks prior to Screening endoscopy.
- UC-related antibiotics must be stopped at least 2 weeks prior to Screening endoscopy.
- Infliximab, adalimumab, golimumab, anti-TNF biosimilars, ozanimod, mirikizumab must be stopped at least 8 weeks prior to Screening endoscopy.
- Vedolizumab and ustekinumab or their biosimilars must be stopped at least 12 weeks prior to Screening endoscopy.
- Non-steroidal anti-inflammatory drugs (NSAIDs) must be stopped at least 1 week prior to Screening endoscopy and during the study (except topical NSAIDs and the use of low dose aspirin for cardiovascular [CV] protection or short course [less than 7 days] of NSAIDs for AE treatment).
- Traditional medicine (e.g., Chinese medicine) must be stopped at least 2 weeks prior to Screening endoscopy.
- Tofacitinib, filgotinib, upadacitinib, etrasimod must be stopped at least 2 weeks prior to Screening endoscopy.
- Antidiarrheals and motility agents (e.g., loperamide, diphenoxylate with atropine) must be stopped at least 2 weeks prior to Screening endoscopy. Any use of antidiarrheals for acute and severe diarrhea must be documented in the dedicated eCRF.
- Probiotics, fish oil must be stopped at least 2 weeks prior to Screening endoscopy.
- [redacted]
- Natalizumab or any other α4β1 integrin agonist: no previous exposure allowed.
- Drugs with mechanism of action that may interfere with the assessment of obefazimod efficacy in the treatment of UC (e.g., IL-6 inhibitors, IL-17 inhibitors, anti-CD20). Please systematically refer to your study Medical Monitor.
- [redacted]
- [redacted]
- [redacted]
- Any newly approved drug for UC during the study must be stopped at least 5 half-lives prior to Screening endoscopy.
- Use of any investigational or non-registered product is prohibited within 3 months or within 5 half-lives preceding baseline, whichever is longer and during the study.
- Parenteral or enteral nutrition must be stopped at least 3 weeks prior to Screening endoscopy.

Prohibited Procedures:

- Total or subtotal colectomy.
- Diverting ileostomy, or colostomy.
- Any other surgical procedure related to the treatment of UC.
- Non-medicinal procedures (e.g., plasmapheresis, cytapheresis, fecal transplantation) regardless of the indication.

4.4.3 Transitioning Subjects from Previous Clinical Trials

Recruiting subjects having taken part in a previous clinical trial is allowed provided adapted wash out period was applied as specified in this CSP (Section 4.3.2). These subjects will be handled as follows:

- The investigational drug used in the previous trial is a non-approved advanced therapy for UC regardless of the trial design (i.e., double blind placebo-controlled, open label extension): subjects will not be considered as having been exposed to this advanced therapy.
- The investigational drug used in the previous trial is an approved advanced therapy in at least one country for UC and the subject is known to have received the drug (i.e., unblinded double blind placebo-controlled, open label extension): subject will be considered as having been exposed to advanced therapy, and considered as advanced therapy inadequate response only in case of a lack or loss of effect or intolerance to the investigational drug.

4.5 Contraception

[redacted]WOCBP should not be administered obefazimod until pregnancy is excluded and should use at least one highly effective method of contraception (failure rate < 1% when used consistently and correctly) depending on their country, during therapy with obefazimod and through the 4-week safety follow-up procedures.

For the purposes of this protocol, female subjects must be of non-childbearing potential or must follow the contraceptive guidelines as specified.

4.5.1 Women of Non-childbearing Potential

Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

- Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)

All other female subjects will be considered to be of childbearing potential.

4.5.2 Women of Childbearing Potential (WOCBP)

WOCBP inside USA:

WOCBP subjects in the USA (and where appropriate per local requirements) who, in the opinion of the investigator, are biologically capable of having children and who may be sexually active,[redacted](failure rate < 1% per year when used consistently and correctly [i.e., perfect use]) for the duration of the active treatment period and through the 4-week safety follow-up procedures.

The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. In addition, the investigator will instruct the subject to call the site immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods are defined as follows:

WOCBP within the USA
[redacted] **effective methods of contraception must be used by WOCBP (USA)**
▪ Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive method for an adequate period of time to ensure effectiveness.

- Correctly placed intrauterine device (IUD).
- Male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository).
- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
- Male sterilization with documented absence of sperm in the post-vasectomy ejaculate.
- In the US, true abstinence applies only to WOCBP who do not have male partners and are not engaging in heterosexual intercourse as their preferred and usual lifestyle. Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable. During the entire duration of the study, these women will take part in a monthly counseling program that will instruct on how to adhere to true abstinence practices.

WOCBP Outside USA:

All WOCBP subjects outside USA and where appropriate per local requirements, must commit to use two effective methods of contraception, [redacted] consistently and correctly for the duration of the active treatment period and through the 4-week follow-up procedures. Contraception methods considered effective and highly effective are defined below. The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in consistent and correct use. In addition, the investigator will instruct the subject to call the site immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

WOCBP must avoid pregnancy throughout the whole study drug period and through the 4-week follow-up procedures after the last dose of study medication.

Highly effective and effective methods of contraception are those that, alone or in combination, result in a failure rate of < 1% per year when used consistently and correctly (i.e., perfect use) and are listed below:

WOCBP – Outside the USA	
Highly effective methods of contraception	**Effective methods of contraception**
▪ Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 28 days prior to Day 1 of study drug. ▪ Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 28 days prior to Day 1 of study drug. ▪ Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure) ▪ Vasectomized partner(s) provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the trial subject. ▪ Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS).	▪ Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 28 days prior to Day 1 of study drug. ▪ Male or female condom with or without spermicide. ▪ Cap, diaphragm, or sponge with spermicide. ▪ A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier method).

- Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.
- True abstinence is not recommended as a highly effective method of contraception but can be applied in countries where accepted only if the following definition is met: true abstinence applies only to non-sexually active WOCBP, or WOCBP who do not have male partners and male participants who are not engaging in heterosexual intercourse as their preferred and usual lifestyle. However, periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable.
- For these subjects, to support subject adherence to true abstinence as a contraceptive method for the duration of the trial, site staff must discuss at each visit and in a monthly phone call between on-site visits, the importance of absolute and true abstinence, outlining the potential risks while taking the study drug during pregnancy.

Female subjects must not donate eggs (ova, ovocytes) as long as contraception is required.

4.5.3 Male subjects

Sexually active male subjects participating in this study should use condoms for the duration of the active treatment period and through the 4-week safety follow-up procedures after the last dose of study medication.Male subjects must not donate sperm as long as contraception is required.

Vasectomy is considered as an adequate method of contraception.

4.5.4 Pregnancy Testing

Female subjects of childbearing potential will commit to be tested for pregnancy at screening, at baseline and at monthly timepoints throughout the treatment period and in the month following EOT (or more frequently if required by local regulations, if a menstrual cycle is missed or if potential pregnancy is otherwise suspected).

At baseline and at Week 8 a serum test will be performed in addition to the urine test. Urine β-hCG testing kits will be supplied by the central laboratory using methodology with a testing sensitivity of at least 25 mIU/mL. If at any point there is a case of a positive urine β-hCG test, the subject will have study drug interrupted and a serum sample will be submitted to the central laboratory for β-hCG testing. If the serum test confirms a positive result, the subject will be withdrawn from the study and all the necessary follow up will be conducted as per Section 8.3.2. If the serum test is negative, the subject may resume study drug.

Should the partner of a male subject become pregnant, investigators will also collect pregnancy information. A specific informed consent will be collected from the pregnant partner to allow data collection.

5 Study Assessments and Procedures

5.1 Schedule of assessments

Table 2: Schedule of assessments (SoA)

	SCREENING	INDUCTION			SAFETY[A]
Time in weeks	W-4	Baseline	W4	W8 / EoT[N]	EOS (4 weeks after last dose)
Time in Days	D-28	D1	D28	D56	D 84
Time Window		± 0 days	± 2 days	-3/+5 days	± 4 days
Obtained Inform Consent	X				
Check of IN/EX Criteria	X	X			
Demographic data [B]	X				
Medical History	X				
Disease History [C]	X				
Extra Intestinal Manifestations	X	X		X	
Previous and Concomitant Medications [D]	X	X	X	X	X
Physical Examination including weight measurement	X	X	X	X	X
Height Measurement	X				
Vital signs	X	X	X	X	X
Stool sample for pathogens	X				
Tuberculosis (TB) & HCV, HBV, HIV	X				
Randomization		X			
IMP dispensation		X	X		
Used blisters collection & Drug accountability			X	X	
Pregnancy test (WOCBP) [E]	X (urine)	X (urine + blood)	X (urine)	X (urine + blood)	X (urine)
[redacted]					
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
Hematology + Biochemistry [G]	X	X	X	X	X
Blood samples drug PK[H]		X	X	X	
Blood sample Cytokines		X	X	X	
Samples for miRNA (Biopsy RNA Later)	X			X	
Samples for miRNA (Blood PAXgene tube)		X	X	X	
Fecal calprotectin [I]		X	X	X	
Modified Mayo Score (pMMS/MMS)	X[†]	X	X	X	
Colonoscopy/sigmoidoscopy [J] with biopsies	X			X	
Subject Questionnaires [K]					
e-Diaries data review/ collection	X	X	X	X	
IBDQ		X		X	
EQ-5D		X	X	X	
WPAI		X		X	

Table 2: Schedule of assessments (SoA)

	SCREENING	INDUCTION			SAFETY[A]
Time in weeks	W-4	Baseline	W4	W8 / EoT[N]	EOS (4 weeks after last dose)
Time in Days	D-28	D1	D28	D56	D 84
Time Window		± 0 days	± 2 days	-3/+5 days	± 4 days
FACIT-Fatigue		X		X	
[redacted]					
UC-related ER, surgery, hospitalization		X			
Adverse Events recording (Including AESI) [M]	X				

AESI = adverse event of special interest; CPK = creatine phosphokinase; [redacted] EOT = end of treatment: EOS = end of study; D = day; EX = exclusion; EQ-5D = Euro Quality of Life – 5 Dimensions questionnaire (5-level); FACIT = Functional Assessment of Chronic Illness Therapy; HBV = hepatitis B virus; HCV = hepatitis B virus HIV = human immunodeficiency virus; IBDQ = Inflammatory Bowel Disease Questionnaire; IN = inclusion; miRNA = microRNA; MMS = modified Mayo score; [redacted] PK = pharmacokinetic(s); pMMS = partial modified Mayo score; TB = tuberculosis; W = week; WOCBP = women of childbearing potential; WPAI =Work Productivity and Activity Impairment questionnaire

A Safety follow-up at the end of the induction phase is only applicable to subjects who do not take part in the maintenance study.

B Including race/ethnicity.

C Disease history includes: disease extent, date of diagnosis, previous medication for UC as per Section 4.4.1 and Section 4.4.2, inadequate response to advanced therapies (lack or loss of response, intolerance) and current activity.

D Previous and concomitant medications will be recorded. All prohibited medication will be checked to ensure the proper wash-out period application (see Section 4.4.2). [redacted] will be collected as well.

E All WOCBP will be tested for urine β-hCG at screening, at baseline and at monthly timepoints throughout the treatment period and in the month following the end of the study treatment visit (or more frequently if required by local regulations, if a menstrual cycle is missed or if potential pregnancy is otherwise suspected). At baseline and at Week 8 a serum test will be performed in addition to the urine test.

[redacted]

G At Day 1, subject eligibility can be confirmed upon the blood results obtained from samples taken at screening. It is mandatory to have the results of all laboratory-based inclusion/exclusion criteria. Ideally, samples will be collected in fed conditions.

H [redacted] At each time point collection (D1, D28, D56) samples will be taken as follows:

- for group 1: pre-dose, 0.5, 1.5, 3 h (and 6 h and/or 10 h if possible) post-dose.
- for group 2: pre-dose, 1, 2, 4 h (and 8 h and/or 12 h if possible) post-dose.

A time window of ± 10 minutes is allowed for each time point collection.

Allocation to either group 1 or group 2 will be determined randomly by the IWRS.

I Stool samples for fecal calprotectin testing should either be taken the day before the visit or in the morning of the on-site visit. Enough collection tubes should be given to the subjects at screening visit. Fecal calprotectin value will remain blinded until the end of the study.

J A full colonoscopy should be performed at screening. Sigmoidoscopy may be performed instead of a full colonoscopy in case of recent colonoscopy dated **less than 3 months from the screening and** if that full colonoscopy report contains: 1) UC extension, 2) lack of colonic cancer, 3) lack of low grade or high-grade dysplasia adenomatous polyps (fully removed or not).

The site staff will apply the appropriate washout period for previous UC medication before the screening endoscopy. **The screening endoscopy is recommended to be performed after the rectal bleeding subscore is confirmed to be ≥1 and the blood results confirming subject's eligibility are obtained.** At week 8, a flexible sigmoidoscopy will be performed. The allowed window for the endoscopy is **- 3 days** to ensure the results are available at Week 8 or soon after Week 8 and limit the risk of treatment interruption between induction and Maintenance. **Results must be available to enter the maintenance study.**

†: pMMS is calculated once within a week prior to screening endoscopy and MMS is calculated following endoscopy.

K IBDQ, EQ-5D and WPAI should be collected prior any other study assessment.

[redacted]

M All AE/AESI must be recorded since the informed consent signature as per dedicated Section 8 of the protocol.
N Subjects in early termination must undergo through the same evaluations as for Week 8 except: PK, cytokines, and miRNA assessments.

5.1.1 Future research

Subject to local regulations and IRB/IEC approval, subjects will be asked to agree to potential future research on any leftover study samples. The objective of future research is to further precision medicine research for the treatment of IBD. Subjects will be informed of why they are being asked to allow the use of their leftover samples for future research and how their samples may be used for future research. Subjects will be given the option to consent to allowing their samples to be used for future research. Subjects who do not wish to participate in this optional future research may still participate in the study.

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. The visit date should always be calculated from Day 1.

Study procedures and their timing are summarized in the above SoA (Table 2).

Protocol waivers or exemptions are not allowed.

The informed consent collection procedure will be duly documented in the subject medical chart (See Section 10.3).

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements.

In accordance with local regulations, subjects who were minor and signed an assent form at the time of joining the trial, and who reach legal age of consent during the course of the trial will be required to re-consent and sign the main consent form to continue participation in the trial.

An exemplary (original or copy) of the signed informed consent form (ICF) will be given to the subject and the original will be placed in the subject's medical record.

In the current study, subjects will be asked to sign the core study ICF, and wherever applicable the General Data Protection Regulation related ICF [redacted]

Adherence to the study design requirements, including those specified in the SoA (Table 2), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator or his/her designee will maintain an enrollment log to record details of all subjects enrolled and to confirm eligibility or record reasons for screen failure, as applicable.

A 7-day extension of the screening may be allowed under strict conditions related to uninterpretable or missing results. The issuance of the 7-day extension for a repeat of the exams or for endoscopy report reception can only be provided in writing by the Sponsor or medical monitor.

5.3 Detail of the Study Assessments

5.3.1 Physical Examination and Vital Signs

A complete physical examination will be performed at each study visit.

Physical examinations will include the eyes, ears, nose, throat, lungs/thorax, heart/cardiovascular system, abdomen, skin and mucosae, nervous system, lymph nodes, musculoskeletal system, and, if applicable, other parts of the body. Any new clinically relevant finding compared to baseline must be recorded in the dedicated section of the eCRF and documented as an AE when clinically significant in the investigator's judgment. The subject's height will be measured at screening only, while subject's weight will be measured at each study visit.

Measurements of vital signs will be performed at each visit (blood pressure, heart rate, body temperature). The subject should rest for at least 5 minutes prior to measurements. The measurements can be performed either in a sitting or supine position. 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 excursion assessed as clinically significant, the investigator must document the change as an AE in the eCRF dedicated pages.

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

5.3.2 EIMs

Investigators will check for the presence of extra intestinal manifestations (EIMs) as defined in Section 2.1, at the timepoints shown in the SoA (Table 2) and will report them on the dedicated eCRF pages.

Any clinically significant changes, according to the investigator judgement, from the previous visit will be recorded as adverse events.

5.3.3 [redacted]

[redacted]

5.3.4 Electrocardiogram (ECG)

Electrocardiograms (ECGs) will be performed at screening, baseline, and Week 8. All ECGs will be performed and read locally. Should the results be abnormal at Week 8, another ECG will be taken during the safety follow-up visit.

A 12-lead ECG with recordings of at least 6 action potentials in Lead II (paper speed 25 mm/s, amplitude 10 mm/mV) will be measured either in a sitting or supine position. Once a position has been chosen for a patient, all measurements will be performed for that patient in the same position. Prior to the recording the subject should be at rest for at least 5 minutes.

The ECG printout will be reviewed by the investigator, then signed, dated, and attached to the medical file. QT, QTc [Fridericia], PR and QRS intervals (msec) from the ECG device will be reported in the eCRF.

Original ECG printouts are considered as source data and should be stored at site. If thermal paper is used, a copy of the original ECG must also be kept.

All abnormal findings must be documented in the eCRF. Any clinically relevant findings must be documented as adverse events.

An increase in QT/QTc to >450 ms for males or >460 ms for females, or of >60 ms from baseline values may be considered for potential discontinuation of a subject from the study.

5.3.5 [redacted]

[redacted]

5.3.6 Colonoscopy/Sigmoidoscopy with Rectal/Sigmoidal Biopsies

Sigmoidoscopy procedures (or colonoscopies if applicable) will be standardized for optimized video acquisition at clinical sites. Endoscopies should be performed according to the Central Imaging Management System Charter. The procedure for bowel preparation will follow site standards. Subjects will receive precise information for adequate bowel preparation.

A 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 central readers who are blinded to the treatment and visit sequence of the recordings.

All procedure videos collected for outcome evaluation will be scored and results communicated within 4 business days.

A full colonoscopy with biopsies will be performed during the screening period at adequate distance of the screening visit to make sure the subject had enough time to report symptoms in the e-Diaries. Endoscopy will be recorded, and videos will be transferred for central reading. The score assessed by the central reader will determine subject's eligibility. Therefore, the site staff will ensure the examination is performed in the appropriate timeframe. A full colonoscopy should be performed at screening (sigmoidoscopy may be performed instead of a full colonoscopy in case of recent **[less than 3 months from the time of initiation of screening]** colonoscopy if the full colonoscopy report contains: 1) UC extension, 2) lack of colonic cancer, 3) lack of low grade or high grade dysplasia adenomatous polyps (fully removed or not).

At screening, appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the investigator, must be available to confirm the subject's eligibility for the study. If this documentation is not available, diagnostic biopsies must be performed during the Screening endoscopy and read by a qualified local pathologist and the results reviewed by the investigator. The central laboratory will not provide a pathology report during the screening endoscopy to document UC diagnosis. Biopsies to rule out adenomatous polyps and colonic cancer may be taken per the investigator's discretion during any endoscopy performed during this study and evaluated by the local pathologist. Biopsies sent to the central laboratory will not be returned to sites and will be retained for study use only. Obtainment of biopsy samples should also be recorded on the video.

For each screening and W8 visit, one type of biopsy has to be collected; the only allowed location in the clinical study protocol are rectum or sigmoid colon.

During all endoscopies, 5 colonic biopsies are to be collected for histologic and miR-124 assessment. At screening, the tissue must be collected from the most inflamed area (rectum and sigmoid), to quantify the degree of the histological damage. If the area is ulcerated, the sample should be obtained from the edge of the ulcer. At Week 8, the biopsy must be collected close to the same area for the screening visit. For all histology biopsies, the location of the biopsy specimen (segment) should be recorded.

At Week 8 if lesions are healed, biopsies should be taken from approximately the same area as the screening endoscopy. Biopsies will be sent to central laboratories for assessment according to Geboes Scoring Scale (refer to the laboratory manual) and for miRNA-124 determination (RNA later). All investigators will follow the same processes for biopsy collection and preparation. These standardized procedures are described in the study laboratory manual. Analysis of biopsies will be performed according to the dedicated Central Laboratory Manual.

Caution: the window allowed to perform the endoscopy at Week 8 is -3 days (maximum). Expedited review timelines will be applied to limit the risk of treatment interruption between induction and maintenance studies.

5.3.7 Patient Reported Outcomes (PROs)

5.3.7.1 Stool Frequency and Rectal bleeding

The stool frequency and rectal bleeding sub-scores assessment will be based on the Mayo scoring system (Section 13.2). Although the physician global assessment (PGA) is performed as part of the subject care, only the pMMS and MMS will be assessed as endpoints according to regulatory guidance (11-13).

Stool frequency and rectal bleeding score will be recorded from the subject e-Diaries at each subject visit.

Subjects will report the number of stools daily, which will be automatically translated in an SFS.

Subjects will report rectal bleeding daily. A daily bleeding score represents the most severe bleeding of the day.

Mayo subscores (RBS and SFS) will be calculated (average) using preferably the 3 consecutive days prior to bowel preparation or the 4 non-consecutive days within 7 days prior to bowel preparation. As a last resort, the 3 consecutive days after endoscopy (excluding the first day post-endoscopy) may be used for calculation.

Subscores will be set to missing if subjects do not have sufficient daily data as described above. As a result, Mayo composite scores (MMS and pMMS) will also be set to missing.

5.3.7.2 Bowel urgency questionnaire

BU will be reported by the subject [yes or no] in an electronic diary (e-Diaries) using a handheld device and recorded daily using a 24-h recall period.

BU will be assessed based on the total number of days on which a subject experiences bowel urgency measured over 3 consecutive days before each study visit.

5.3.7.3 Nocturnal bowel movement

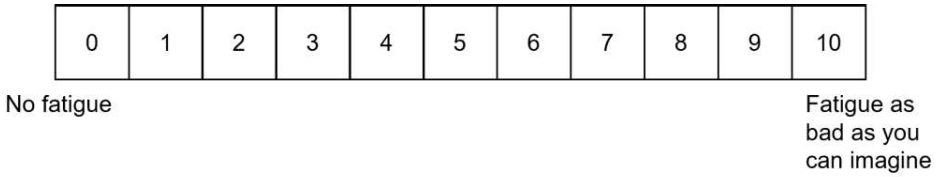
NBM (one or more sleep interruption due to bowel movement) will be reported by the subject [yes or no] in an e-diaries using a handheld device and recorded daily using a 24-h recall period.

NBM will be assessed based on the total number of days on which a subject experiences NBM measured over 3 consecutive days before each study visit.

5.3.7.4 Fatigue- Numeric Rating Scale and FACIT-Fatigue

The fatigue NRS is a subject-reported, single-item, 11-point horizontal scale anchored at 0 and 10, with 0 representing 'No fatigue' and 10 representing 'Fatigue as bad as you can imagine' (Figure 4). Subjects are asked to 'please rate your fatigue (weariness, tiredness) by selecting the number that describes your worst level of fatigue during the past 24 hours.

Figure 4: Fatigue Numeric Rating Scale



The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue is a subject-reported 13-items questionnaire that assesses the subject fatigue in chronic diseases (Section 13.6).

5.3.7.5 Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is a widely used questionnaire for health-related quality of life assessment in subjects with IBD. This questionnaire has been adapted and validated into several languages. IBDQ will be completed by the subjects at the timepoints shown in the SoA (Table 2), and prior to any study procedures (see Section 13.3 for the full questionnaire).

5.3.7.6 EuroQoL-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L is a generic preference-based questionnaire validated for the assessment of health-related quality of life in IBD subject population. It covers 5 dimensions: mobility, self-care, usual activity, pain and discomfort and anxiety/depression.

Subjects are required to rate each dimension on 5 levels, reflecting no problem, some problem, and extreme problem. The dimensional scores are subsequently used to derive a utility score.

The questionnaire also includes a 20-cm visual analogue scale (VAS) that allows subjects to rate their state of health by drawing a line from an anchor box to the point on the VAS which best represents their health on that present day. The minimum clinically important difference of EQ-5D-5L utility score and VAS are 0.08 and 10 points respectively.

EQ-5D-5L will be completed by the subjects at the timepoints shown in the SoA (Table 2), and prior to any study procedures (see Section 13.4 for the full questionnaire).

5.3.7.7 Work Productivity and Impairment (WPAI) questionnaire

The WPAI questionnaire measures impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as the impairments in unpaid activity due to health problem during the past seven days. It has been validated to quantify work impairments UC and CD.

The WPAI:UC consists of six questions: 1 = currently employed; 2 = hours missed due to UC; 3 = hours missed other reasons; 4 = hours actually worked; 5 = degree UC affected productivity while working (using a 0 to 10 VAS); 6 = degree UC affected productivity in regular unpaid activities (VAS).

The recall period for the questions 2 to 6 is 7 days.

Four main outcomes generated from the WPAI:UC are:

- percent work time missed due to UC.
- percent impairment while working due to UC.
- percent overall work impairment due to UC.
- percent activity impairment due to health Q6/10 for all respondents.

WPAI:UC questionnaire will be completed by the subjects at the timepoints shown in the SoA (Table 2), and prior to any study procedures (see Section 13.5 for the full questionnaire).

5.3.8 Laboratory Parameters

All parameters will be assessed by a central laboratory, except urine pregnancy test. Laboratory assessments will be conducted at the timepoints shown in the SoA (Table 2).

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, s/he will consult with the Sponsor medical monitor.

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

Table 4 lists all the clinical laboratory parameters that must be measured and the central laboratory responsible for each analysis.

Table 4: Laboratory Tests

Analysis	Parameters
Hematology	RBC, hematocrit, hemoglobin, WBC (absolute & differential), platelet count, INR, fibrinogen, prothrombin, neutrophils, lymphocytes, monocytes, eosinophils, basophils
Biochemistry	Sodium, potassium, chloride, calcium, phosphate, glucose, BUN or urea, creatinine, creatinine clearance, AST/ALT, [redacted] ALP, GGT, LDH, CPK, total cholesterol, HDL cholesterol, LDL cholesterol (Direct), triglycerides, total bilirubin, total protein, albumin, β-hCG (for WOCBP only), hs-CRP, FSH
[redacted]	[redacted]
Other	Fecal calprotectin*
Serology (Screening only)	HBsAg, anti-HBs Ab, anti-HBc Ab, anti-HCV Ab, anti-HIV Ab, HBV DNA, HCV RNA.
Parasitology (Screening only)	Bacteria, ova and parasites
Cytokines analysis	[redacted] (non-exhaustive panel)
miR124 modulation (blood)	
miR124 modulation (biopsies)	
Pharmacokinetic	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBsAb=anti-Hepatitis B antibody; anti-HBc Ab = Anti-Hepatitis B core antibodies; anti-HCV ab=anti-Hepatitis C virus antibody; anti-HIV ab=anti-human immunodeficiency virus antibody; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; CPK=creatine phosphokinase; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HBsAg=Hepatitis B surface antigen; HDL=high density lipoprotein; hsCRP=high sensitivity C-reactive protein; [redacted] INR=international normalized ratio; LDH=lactate dehydrogenase; LDL=low density lipoprotein; [redacted] RBC=Red Blood Cells; [redacted] WBC=white blood cells.

* Stool samples for fecal calprotectin testing should either be taken the day before the visit or in the morning of the on-site visit. Enough collection tubes should be given to the subjects at the Screening Visit. Subjects will be instructed how to store adequately the samples as per Laboratory Manual. Fecal calprotectin value will remain blinded until the end of the study.

Subjects should arrive in a fed state at the site for the blood sample collection.

For safety reasons, repeated tests performed locally are acceptable for all hematology and all biochemistry (except hs-CRP) parameters, Clostridium difficile (toxins A and B), Tuberculosis (QuantiFERON-TB Gold Plus), serology and parasitology, as well as [redacted] should the central laboratory results be missing or not interpretable. Every request to use local test must be approved by Sponsor designee and/or study medical monitor prior to proceeding.

For PK timepoints collection (D1, D28 and D56), subjects should take the study drug on site after the pre-dose samples have been taken.

5.3.8.1 Tuberculosis and QuantiFERON-TB Gold Plus test

All potentially eligible subjects will be tested for tuberculosis (TB).

Subjects with current active TB, or current non treated latent TB infection at screening are excluded from the study.

Subjects diagnosed with latent TB at screening, ruled out for active TB are assessed as screen failure. In order to be eventually re-screened, they must have received at least 4 weeks of an appropriate TB prophylaxis treatment per national/local medical guidelines or World Health Organization guidelines (the treatment course should be continued during the study to ensure adequate completion). In that case only, positive QuantiFERON-TB gold plus test is accepted.

Depending on the result of the QuantiFERON-TB Gold Plus test the following may apply:

- The result of the re-test is negative for TB: then the screening procedure can continue.
- The result of the re-test is positive for TB: the subject is assessed as screen failure. In that case the subject may be re-screened as detailed above.

- The result is intermediate: a re-test is allowed. Should the result of the re-test be still intermediate again, the site staff contacts the Sponsor Medical Monitor for further guidance.

Caution: [redacted] is prohibited (see Section 13.1 and Section 4.4.2).

5.3.8.2 Clostridium difficile

During the Screening period a stool sample will be collected and sent to the central laboratory for testing. The sample will be assessed for the presence of *C. difficile* toxins by the central laboratory. Additional information is available in the Laboratory Manual provided by the central laboratory.

Subjects who are negative for *C. difficile* toxins can continue screening procedures.

Subjects who are positive for *C. difficile* toxins should be screen-failed; these subjects may be re-screened after completing the appropriate treatment. For subjects who are borderline for *C. difficile* toxins, the investigator may send another sample for a test. If the result is negative, the investigator may consider the test to be negative based on his/her judgment. If the result is positive or borderline, the test is considered positive, and subject should be screen failed.

5.3.9 Volume of Blood Sampling

Table 5 summarizes the volume of blood to be sampled at each study visit. The total (maximal) volume of blood taken from a participating subject is 2.5 to 36.7 mL per on-site study visit, meaning up to 174.2 mL in total. If a repeat test is required at a local laboratory, an additional of 2.5 to 36.7 mL per test may be required, meaning up to a total of 348.4mL.

Table 5: Blood Volume

Required volume from Screening to EOS	***SCR***	***BL/D1***	***W4/D28***	***W8/D56***	***EOS D84***	***EOT***	***LFT***	***TOTAL***
	V1	**V2**	**V3**	**V4**	**V5**	**-**	**-**	
Total per visit (mL)	36.7	Up to 36.2	Up to 35.2	Up to 36.2	13.2	14.2	2.5	Up to 174.2

BL = baseline; D = Day; EOT = End of Treatment; EOS = End of Study; LFT = Liver Function Test; SCR = Screening; V = Visit.

5.3.10 Unexpected Situations and Acceptable Protocol Modifications

In the specific situation of the COVID-19 pandemic, where subjects and site staff cannot comply with the protocol requirements, some adaptations might be allowed as long as these adaptations are duly authorized by local regulations and approved by regulatory authorities and IEC-IRBs, such as:

Direct dispensation of the study medication to subject
Only possible for Week 4 visit.

Home healthcare service
The involvement of home healthcare services and local laboratories for sample analysis may also be considered where relevant and allowed by local legislation.

Laboratory analysis
If a subject is unable to attend a visit where laboratory samples are collected, it is recommended to perform all scheduled tests at a local laboratory, except for hs-CRP, PK, FC, and cytokine analysis.
Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. The results should be reviewed by the investigator and clinically significant abnormal results should be documented in electronic data capture (EDC) as an unscheduled laboratory test as soon as possible.

6 Investigational Product(s)

All investigational products to be used in this study have been manufactured, packaged and labelled by contract manufacturers for the Sponsor, according to Good Manufacturing Practice (GMP) standards and are supplied to investigators free of charge. Prior and concomitant medications are described in Section 4.4.

6.1 Description of the Investigational Treatment

The IMP is defined as obefazimod, or its matching placebo, and is intended to be administered to a subject according to the study protocol. The IMP details are shown in Table 6.

Table 6: Investigational Medicinal Product Details

INN:	Obefazimod	Placebo
Dosage Formulation:	[redacted]	
Chemical Name:	8-chloro-*N*-[4-(trifluoromethoxy)phenyl]quinolin-2-amine or (8-chloro-quinolin-2-yl)-(4-trifluoromethoxy-phenyl)-amine	NA
Dosage Level/Unit Dose Strength:	25 mg capsule 50 mg capsule	NA
Route of Administration:	Oral	
Dosing Instructions:	25 mg regimen: 1 capsule of obefazimod 25 mg per day 50 mg regimen: 1 capsule of obefazimod 50 mg per day	1 capsule of placebo per day
Packaging and Labeling:	Capsules are packaged in [redacted] Each blister card will be labeled as per country requirements. Each blister card (=kit) contains 35 capsules.	
Storage conditions:	[redacted] The IMP should not be used beyond the expiration date. Drug supplies are to be stored in a secure, limited-access location under the storage conditions required by GCP/GMP guidelines.	
Site responsible of manufacturing and control the capsules:	[redacted]	
Site responsible of packaging and labelling:	[redacted]	
Site responsible of packaging and labelling (alternative site)	[redacted]	

GCP = Good Clinical Practice; GMP = Good Manufacturing Practice; IMP = investigational medicinal product; [redacted]

6.2 Administration and Dosing

6.2.1 Administration of the Investigational Product

Depending on the randomization, subjects will be given a daily dose of either obefazimod 50 mg or obefazimod 25 mg or a matching placebo. All subjects regardless of the treatment group will receive 1 capsule every day:

- Obefazimod Daily dose 50 mg: 1 capsule of obefazimod 50 mg
- Obefazimod Daily dose 25 mg: 1 capsule of obefazimod 25 mg

- Placebo: 1 capsule of matching placebo

Subjects will be orally dosed daily in a fed condition (ideally at the same time in the morning) with a glass of water. An e-Diaries, in which the subject should report the time for study drug intake from baseline visit onwards, will be given to the subject.

On Day 1, on the day of Week 4 and Week 8 visits, pre-dose blood sample for obefazimod and ABX464-N-Glu concentration analyses must be taken before the subject takes the study drug. On those days, subjects will be instructed to take the study drug on site once the pre-dose blood sample is taken.

6.2.2 Guidelines for Treatment Postponement and Dose Modifications

No dose escalation/dose adjustments are allowed.

6.3 Method of Assigning Subjects to Treatment Arms

All subjects will be assigned a unique (i.e., reallocation of the ID will not be permitted) and incremental Subject Identification (ID) number assigned according to the subject's order of inclusion in the center.

Eligible subjects will be randomized according to a 1:1:2 ratio to matching placebo, obefazimod 25 mg, or obefazimod 50 mg. Randomization will be performed via IWRS, and will be stratified according to the following criteria:

- Subjects with inadequate response to advanced therapies (Yes/No)

  NB: Subjects with previous exposure to advanced therapies but without a proper documentation of the inadequate response to these advanced therapies will be randomized into the "No" strata.

- Subjects with concomitant oral CS at baseline (Yes/No)

Treatment will be allocated as per randomization list.

In all cases, subjects should return their used and unused blister cards at each study visit for a compliance check.

6.4 Blinding and Breaking the Study Blind

IMP will be packaged in child-resistant blister cards with blinded labels. Blister cards will be numbered according to a randomized treatment number list. The content of the labeling is in accordance with the required references listed in the GMP.

The investigator, study personnel, and study participants are blinded with respect to double blinded treatment (i.e., obefazimod or placebo). The Sponsor will assign an independent third party who will generate the randomization list and the corresponding treatment. The Sponsor will have no access to that information during the study.

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

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

Details of any emergency or unintentional unblinding shall be documented fully in the Trial Master File (TMF) and Investigator/Pharmacy Site File. The Sponsor should be notified of the unblinding and be provided with the subject number but NOT the result. The details shall be included in the statistical report.

6.5 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 IWRS web-based drug accountability and returns management (DARM). Accuracy of the accountability will be monitored by the Clinical Research Associate (CRA).

Empty, partially used and unused medication blister cards will be destroyed on site in all sites where applicable providing they have adequate documentation of the destruction performed.

Before site close-out, empty, partially used or unused treatment medication can be returned to the central depot(s) for destruction or destroyed locally. A rigorous accountability of the used and unused treatments left on-site must be performed by the CRA before giving an agreement for the destruction of the study drug, unless required otherwise by local policies.

7 Study Completion

7.1 Subject Completion

IMP intake shall continue throughout the Induction phase, except if the subject fulfils a premature discontinuation criterion (defined below). The last dose of the Induction study will be taken on site, on the day of the last visit (D56 ± 2 days). After End of Treatment visit assessments, completed subjects eligible for maintenance will be encouraged to take part in the ABX464-107 maintenance study (no procedure will be performed prior to subjects informed consent collection). The first treatment dose in the frame of the maintenance study will be taken on the first day following induction D56 visit.

Subjects who do not take part in the maintenance study will be followed as per the site standard of care after the last study visit.

In the event that a subject stops treatment, switches treatment, or violates the protocol, every effort will be made to collect D56 endpoint data, in order to reduce missing data.

7.2 Temporary Treatment Discontinuation

IMP should be continued whenever possible.

In case the IMP must be stopped for any reason and where there is a plan to resume treatment, this period must not exceed 3 days of interruption. Any temporary IMP discontinuation should be documented in the eCRF. Where the IMP is temporarily discontinued the investigator should consult with the Sponsor medical monitor before restarting a subject's treatment.

7.3 Subject Premature Trial Discontinuation

A subject can be withdrawn at any time from the study. Should a subject discontinue the study early, EOT and EOS visits must be performed as per the SoA (Table 2).

Subjects must be discontinued in the following cases:

- An AE or any medically significant abnormal laboratory results that would place the subject at risk as determined by Sponsor Medical team and preclude continuation of treatment.
- Any relevant toxicity or negative change in the risk/benefit assessment leading to an unacceptable risk for the subject (i.e., occurrence of AEs or unexpected and medically concerning deterioration in condition in terms of its severity or frequency, or otherwise a new occurrence in comparison to those AEs listed in the Reference Safety Information per requirements set out in regulation 536/2014 and ICH E2F), or any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment.
- [redacted]
- Severe (grade ≥ 3) infection, severe or serious opportunistic infection, or sepsis.
- [redacted]
- [redacted]
- Abnormal liver enzymes test as below:
  - ALT or AST > 8 x ULN.
  - ALT or AST > 5 x ULN for more than 2 weeks.
  - ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5.
  - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Pregnancy.
- Subject withdrawal of consent.
- Subject significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by investigator and Sponsor Medical team.
- Study termination by Sponsor.

Subject's premature trial discontinuation will also be considered in the following cases:

- Anemia and/or new onset anemia (defined as hemoglobin < 8 g/dL or hemoglobin drops > 2 g/dL from baseline) will be discussed on case-by-case basis with Sponsor Medical team and documented accordingly. Note: transient abnormal values, and/or abnormal values related to an existing condition that do not constitute a medically significant worsening will not be a criterion for discontinuation.
- Protocol deviation (including inclusion/exclusion criteria noted after randomization) or introduction of prohibited medications or dosages, as determined by Investigator and Sponsor Medical team.
- Investigator's decision that can be made at any time during the course of the study, especially in case of UC lack of effect or loss of effect (symptom worsening).

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

7.4 Screen Failures

The subject who does not fulfil the eligibility criteria will be considered a screen failure. An eligible subject is a screen failure if s/he signs the informed consent but withdraws before the randomization procedure at Day 1. All potential subjects who are screened for enrolment in this study will be listed on the subject Screening Log/Identification List. Reasons for screening failure will be recorded for potential subjects who do not enter the study. Minimal subject data should be entered in the eCRF including Informed Consent, screen failure criteria, demographics and any SAEs occurring during screening process.

Based on the investigator evaluation and sponsor prior approval, a non-randomized subject can be rescreened. This re-screening procedure should be documented, the subject should consent again and a new unique and incremental subject Identification number be allocated. If the rescreening takes place within 3 months of the previous screening, a flexible sigmoidoscopy may be substituted for the screening colonoscopy previously performed.

7.5 Stopping Rules

This study may be prematurely terminated if, in the opinion of the Sponsor, there is sufficient reasonable cause. In the event of such action, written notification documenting the reason for study termination will be provided to each investigator.

Circumstances that may warrant termination include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects (e.g., as determined by the IDMC).
- Plans to modify, suspend, or discontinue the development of obefazimod.
- Decisions of Regulatory Authorities or IRB/IEC.
- Other administrative reasons.

In all cases, all necessary measures have to be taken to guarantee appropriate safety follow-up of all patients already included in the trial. Should a subject discontinue the study early, EOT and EOS visits must be performed as per the SoA (Table 2).

The IRB or EC and the Regulatory Authorities will be informed in writing about any termination of the trial.

7.6 Lost to Follow-up

The subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if the subject fails to return to the clinic for a required study visit:

The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

Before the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

See the SoA (Table 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.7 End of Trial

If the last subject takes part in the maintenance study, End of Trial will be based on the last visit of the last remaining subject in the induction study.

If the last subject does not take part in the maintenance study, End of Trial will be the date of the last follow-up of the last remaining participant. In case of last subject is declared lost to follow-up, the date of the last follow-up or the date of the last contact attempt (whichever occurs later) should be considered.

8 AEs, SAEs and AESIs

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

All AEs (serious and non-serious) will be collected from the time of signing of ICF and until either the EOS visit is performed for subjects not entering the Maintenance study (or EOT in case of subjects withdrawing consent), or until their last IMP intake for subjects entering Maintenance.

Incidental findings may include previously undiagnosed medical conditions unrelated to the aims of the study which may be of potential health or reproductive importance to the clinical study subject. During the informed consent process, clinical study subjects may decide whether they want to be notified of any incidental findings. If so, they will be allowed to designate a healthcare professional to receive such findings to help them with the clinical interpretation of the findings and the determination of any follow-on actions. The local investigator will determine whether such a finding should be communicated to the subject, in accordance with local laws and regulations. The clinical study subject will be made aware that neither the Sponsor nor the investigator is responsible for confirming the incidental findings. Nor will they provide medical advice, opinion, nor be responsible for any subsequent healthcare decisions based on the findings.

8.1 Definitions

8.1.1 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.

Fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening, will not be considered AEs.

Note: The official definition also extends to AEs occurring in the placebo arm. For monitoring purposes, events occurring during pre-and post-treatment periods will also be designated as AEs. Therefore, reporting of such events, AEs and SAEs, will start when the subject consents to participate in the study and up to 4 weeks after he or she has completed or discontinued the investigational product. The period after discontinuing IMP may be extended if there is a strong suspicion that the drug has not yet been eliminated.

8.1.2 AESI

The following treatment emergent events will be considered AESIs and must be reported as if they were SAEs as stated in Section 8.7.

[redacted]

[redacted] should be reported as AESIs by the site physician. As described in Section 1.4 the clinical relevance of data from [redacted] is unknown. So far, clinical safety data with obefazimod do not suggest [redacted]

Headaches

Headaches are frequently reported by subjects treated with obefazimod.

Headaches must be reported as an AESI if:

The headache lasts more than 72 hours continuously (or is an intermittent headache with a continuous symptom free period < 12 hours) and is not relieved by painkillers for > 12 hours.

A headache occurring after a remission longer than 12 hours will be considered a “new headache” and reported as such.

Headaches that qualify as AESI will be monitored by means of a Headache questionnaire. The investigator or qualified designee will complete the Headache AESI questionnaire in consultation with the subject together with the AESI form and send them to the sponsor or its designee.

Anemia

[redacted] the Sponsor performs surveillance for anemia by means of regular determination of hemoglobin and hematocrit levels. Anemia is defined as hemoglobin < lower limit of normal (LLN) per sex. Anemia will be reported as AESI if hemoglobin < 8 g/dL or if hemoglobin drops > 2 g/dL from baseline.

Hepatic enzyme elevations

[redacted] Based on nonclinical data, a DILIsym evaluation of obefazimod was conducted and concluded that there was no risk of the drug-induced liver injury (DILI) in these subjects. Analysis of ALT/AST changes in subjects treated with obefazimod, did not reveal any meaningful variation of the mean ALT/AST measurement throughout treatment nor an increased incidence of any liver function tests (LFTs). No Hy’s Law cases have been observed in obefazimod-treated subjects. Sporadic cases of isolated alkaline phosphatase increase have been reported in subjects dosed with obefazimod.

An increase > 3.0 × ULN in liver transaminases (AST and/or ALT) with or without cholestasis or clinical symptoms (elevated alkaline phosphatase) will be reported as an AESI.

Serious or severe (grade ≥ 3) infections and opportunistic infections

[redacted]

Subjects will be monitored for the development of signs and symptoms of infection during treatment with obefazimod.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms (e.g., aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis) and serious or severe (grade ≥ 3) infections will be reported as AESIs.

Study treatment will be discontinued if a subject develops a severe (grade ≥ 3) infection, severe or serious opportunistic infection, or sepsis.

[redacted]

[redacted]

[redacted]

[redacted]

Definition of diagnosis of [redacted]

[redacted]

[redacted] diagnosed per the criteria defined above, in subjects with an exposure to study agent, will be reported as an AESI.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

8.1.3 Definition of Adverse Reactions

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

8.1.4 Definition of an SAE

An SAE (experience) or reaction is any untoward medical occurrence that, at any dose:

- Results in death,

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

- 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.

- 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-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

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

- 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.

- Is a congenital anomaly/birth defect,

- 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.

8.1.5 Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

8.2 Events and/or Outcomes Not Qualifying as AEs or SAEs

UC is associated with certain characteristic signs and symptoms including increased stool frequency and rectal bleeding, that may be present at baseline and persist or fluctuate based on the individual patient's disease history during the course of the study. These signs and symptoms are considered medically anticipated clinical events for the condition under study (i.e., UC) and will not be collected as AEs. These characteristics of disease activity will be regularly captured in the partial Mayo score and will be reviewed by the IDMC. Worsening of disease activity for UC (e.g., clinically significant increase in the daily amount of rectal bleeding and/or stool frequency beyond the patient's normal fluctuation, as judged by the investigator), will be collected as AEs or SAEs and reported according to regulatory reporting requirements. Extra-intestinal manifestations of the patient's disease (e.g., arthralgias, arthritis, uveitis) that develop or worsen during the study are considered AEs.

However, if the event meets the criteria for an SAE, including hospitalization for a flare of UC, it should be reported nonetheless per Section 8.8.

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

- 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 and Clinical assessments

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

8.3.2 Pregnancy Report

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female subject becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.
2. A male has been exposed (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

Subjects who become pregnant at any time will be immediately required to stop treatment and will come for a safety follow-up 4 weeks after the last study dose intake. Post-pregnancy, the subject will be contacted for pregnancy outcome follow-up (see below). A specific consent for the pregnancy outcome follow-up will be sought from the subject, and other parent wherever required per local regulations.

All appropriate withdrawal assessments may be performed at the discretion of the investigator.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator will collect pregnancy information on any female subjects or partner of a male subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on a specific pregnancy notification form and submit it to the Sponsor 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 by investigators to the Sponsor or its designee. Follow-up will normally end 12 months post-pregnancy.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an SAE.

- A spontaneous abortion, miscarriage or stillbirth is always considered to be an SAE and will be reported as such.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard for causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to obefazimod.

The time period for collecting pregnancy outcome information is from the signing of informed consent to 12 months post-pregnancy.

In case of paternal exposure, the investigator will provide the study subject with the Pregnancy Follow-up ICF. The investigator must document in the source documents that the subject was given the Pregnancy Follow-up ICF to provide to his partner.

8.4 Treatment of Overdose

No data are currently available regarding the steps to be taken following an overdose of obefazimod. The subject should be treated symptomatically according to first aid medical principles.

An overdose (accidental or intentional) with the IMP is an event suspected by the investigator or spontaneously notified by the subject (not based on systematic capsule count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

An overdose should be reported as an AE or a SAE according to its severity.

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

The AE, SAE and AESI detection and reporting period starts from the time a subject consent to participate in the study, and continues up to 4 weeks after he or she has completed or discontinued the investigational product and must be recorded in the subject's eCRF.

Importantly, once appropriately recorded in the eCRF within 24 hours of awareness, an automated notification will report all SAEs/AESIs by email to:

E-mail: [redacted]

If the eCRF system is inaccessible due to system maintenance or not working for any reason, the notification will be sent manually by the site to the same email address within 24 hours of awareness.

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

Pregnancy reports (including the site and subject identification numbers) will be sent directly by the site to the sponsor or its designee, using the email address referenced above.

Follow-up of all AESIs will be performed by the study Medical Monitor with site collaboration.

8.6 Recording AEs, SAEs and AESIs

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. The date of AE report and acknowledgement must be recorded. 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 IMP.
- The severity of the sign/symptom or clinically significant abnormal laboratory value according to Common Terminology Criteria for Adverse Events (CTC-AE) Classification 5.0 or more recent version.
- The causal relationship between the investigational product and the occurrence of each AE. This will be assessed by each investigator using clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant medications, other risk factors and the temporal relationship of the event to the investigational product will have to be considered. Causal relationship to study treatment should be identified as Related, Probably Related, Possibly Related, Unlikely Related or Not Related.
- Action taken regarding the investigational product:
    - Dose not changed
    - Drug interrupted
    - Drug withdrawal
    - Not applicable
    - Unknown
- Subject's outcome:
    - Not recovered / not resolved (AE is ongoing)
    - Recovered / resolved
    - Recovered / resolved with sequelae
    - Recovering / Resolving
    - Unknown
    - 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 as new each time.

8.7 Reporting of SAEs/AESIs to the Sponsor or its Designee

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

It is the investigator's responsibility to ensure that the SAE or AESI are captured in the eCRF corresponding page **immediately after becoming aware of the SAE/AESI, within 24 hours of awareness at the very latest.** Once appropriately recorded in the eCRF, an automated notification will report all SAEs/AESIs to the sponsor or its designee as described in section 8.5. Follow-ups will be performed by the study Medical Monitor in close collaboration with the site staff.

The study specific SAE/AESI form should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. When submitting AESI, refer to Section 8.6 for identifying the document that should be sent to the sponsor or its designee together with the AESI form.

The investigator will assess causality between the study drug and the AESI/SAE according to Table 7.

Table 7: Adverse Event Relatedness

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

An assessment of causality should always be provided at the time of the initial report. If the investigator or designee does not have all the information regarding the SAE/AESI, he/she should not wait to receive additional information before completing the form and notifying the sponsor or its designee, using the email address referred in section 8.5.

Any additional new information on a previously reported SAE (=follow-up) should be reported in the eCRF corresponding page within 24 hours of receipt of the information. If the eCRF system is inaccessible due to system maintenance or not working for any reason, the notification will be sent manually by the site to the same email address mentioned in section 8.5 within 24 hours of awareness.

In addition to this, additional information for any reported SAE/AESI can be requested by the Sponsor or its designee. The investigator must respond to these requests for follow-up information or questions regarding the SAE/AESI, within 1 working day for urgent queries or 5 working days for normal queries. The SAE will be followed until the investigator and the Sponsor agree that the event is satisfactorily documented and resolved/stabilized.

8.8 Reporting of SAEs to Regulatory Authorities

The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authorities and other regulatory authorities about the safety of the IMP. It is therefore important that the investigator notifies promptly (within 24 hours of awareness) the Sponsor 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 IEC and, if required, to the relevant government authority.

Safety reports on AEs that are serious AND unexpected AND causally associated with the investigational product are prepared according to the Sponsor'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.

In the EU/EEA, it is the sponsor's (or it's designee's) responsibility to notify the Eudravigilance database of these reports, if applicable, in line with Regulation 536/2014.

In Switzerland, SUSARs will be reported to Swissmedic by the Sponsor (or its designee) according to the provisions under Art. 41 of the Clinical Trials Ordinance (ClinO 810.305).

9 Data Analysis and Statistical Considerations

A summary of the principal features of the statistical analysis of the data is described in this section. A more technical and detailed elaboration of the principal features stated in the protocol will be given in the Statistical Analysis Plan (SAP).

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

9.1 Statistical and Analytical Plans

9.1.1 Generalities

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor.

Descriptive statistics will be used for all variables, as appropriate. Descriptive statistics will be presented by treatment arm for all primary and secondary efficacy variables for each measurement time point.

Continuous variables will be summarized by the number of observations, mean, standard deviation (SD), median, quartiles (first quartile [Q1] and third quartile [Q3]), minimum, maximum. Categorical variables will be summarized by frequency counts, percentages. Unless otherwise stated, percentages will be calculated out of the total population for each treatment group.

For mean change from baseline efficacy analyses, only subjects with a baseline and at least one non missing postbaseline measurement will be included.

Additional details about the statistical methods will be provided in the SAP.

Statistical Hypothesis

The primary objective of the study is to demonstrate efficacy in the obefazimod 50 mg and 25 mg treatment groups, respectively, compared to placebo regarding the primary endpoint.

For all primary and key secondary endpoints, the null hypothesis is no difference between obefazimod 50 mg and placebo, and obefazimod 25 mg and placebo.

[redacted]

Definition of missing data imputation

Missing binary outcome data will be imputed using a non-responder imputation (NRI). In NRI analyses, subjects who have missing efficacy assessment at Week 8 will be considered non-responders with respect to the efficacy endpoint. Missing continuous outcome data will not be imputed for analysis of covariance (ANCOVA) analysis. However, they will be handled by implicit imputation in mixed model for repeated measures (MMRM) analysis.

Imputation rules for AEs and concomitant medications with partial start/stop dates will be outlined in the SAP.

9.1.2 Protocol Deviations

Protocol deviations (PDs) will be reviewed during the study course on a regular basis and classified as critical, major or minor per a separate PD plan. A final review will be performed during the blinded data review meeting. According to ICH E3 and ICH E3(R1), important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Important PDs will be descriptively summarized for the Safety Set.

9.1.3 Definition of Study Analysis Sets

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

- The Screened Set includes all subjects who signed informed consent.

- The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment group to which they were randomized (i.e., "as randomized"), regardless of the treatment received. The efficacy analysis will be based on the FAS.
- The Safety Set includes all randomized subjects who have received at least one dose of study drug. Subjects will be analyzed according to the treatment received (i.e., "as treated"). The safety analysis will be based on the Safety Set, unless specified otherwise.

Additional analysis sets may be defined in the SAP.

9.1.4 Subjects Disposition and Study Drug Exposure

The number and the percentages of subjects included in each analysis set will be tabulated for each treatment group and overall. The reason for subject exclusions from each analysis set will also be listed. In addition, the number and percentage of subjects who completed the study, who discontinued early with their reason for discontinuation will be tabulated.

Exposure to study drug will be summarized for all subjects who have received at least one dose of study drug over the entire study. The duration of study drug treatment will be summarized for each treatment group. The duration of treatment is defined as the difference between the dates of the first and last doses of the treatment plus 1 day. Study drug compliance will be summarized for each treatment group. Compliance is defined as the number of capsules taken (i.e., the difference between the number of capsules dispensed and the number of capsules returned/lost/damaged) divided by the number of capsules a subject is supposed to take for the length of time that the subject was in the Treatment Phase of the study (i.e., date of last dose during Treatment Phase – date of first dose + 1). Blisters with missing data for the number of capsules returned will be excluded from the compliance calculation for the subject. The Safety Set will be used.

9.1.5 Demographic and other Baseline Characteristics

Demographics will be summarized by treatment group. This analysis will be conducted on the FAS.

Medical history by frequencies will be summarized for each treatment group. Prior therapies and medications will include all therapies and medications administered prior to the date of the first dose of study drug. Prior therapies and medications for UC will be summarized for the Safety Set.

Concomitant medications will be summarized for the Safety Set. All medications administered between the date of the first dose of study drug and the end of study, inclusive, (i.e., all medications starting or ongoing during the treatment period) will be included. Thus, all medications with an end date prior to the first dose of study drug dose will be excluded from the summary table. i.e., A subject who reports two or more uses of the same concomitant medication will be counted only once within each generic name. A subject with concomitant medications with more than one generic name will be counted only once in the overall total.

Therapies and medications will be coded using the World Health Organization (WHO) Drug Dictionary. No statistical test will be performed.

9.2 Safety Analyses

Safety analyses will be carried out using the Safety Set by treatment group. Incidence of AEs, including those related to study drug and adverse events of special interest (AESIs), changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be summarized. Treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term for each treatment group. Values and change from Baseline for quantitative laboratory parameters, quantitative ECG parameters, and vital signs data will be summarized.

Missing safety data will not be imputed. No statistical test will be performed.

Additional analysis details will be specified in the SAP.

9.2.1 Treatment-emergent Adverse Events

AEs will be coded using the standard dictionary (Medical Dictionary for Regulatory Activities [MedDRA]) down to the lower-level term. The assessment of safety will be based on the frequency of AEs (with and without regard to causality) graded according to the CTCAE Classification (version 5.0) and, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and potentially clinically significant abnormalities determined upon investigator considerations.

TEAEs will be tabulated with number of subjects, percentages of subjects, incidence rate (IR), and number of AE records. IR is defined as the number of subjects with an AE divided by total exposure, which is defined as the sum of either time (years) from first dose to the onset of first such event for those who experienced this AE, or time (years) from first dose to last participation for those who did not experience this AE. IR will be reported as 1 per 100 subject years by treatment group.

TEAE is defined as any AE which started or worsened in severity from pre-existing AE after the first dose of study drug.

An overall summary table will be presented: any AE, any TEAE, any related TEAE, any TEAE leading to study drug discontinuation, any related TEAE leading to study drug discontinuation, any TEAE leading to study drug interruption, any related TEAE leading to study drug discontinuation, any serious TEAE, death, any related serious TEAE, any Grade 1 TEAE, any Grade 2 TEAE, any Grade 3 or higher TEAEs.

Summaries will be presented by SOC and preferred term for:

- TEAEs.
- TEAEs by maximum severity.
- TEAEs by maximum relationship.
- Serious TEAEs.
- TEAEs leading to study drug discontinuation.
- TEAEs of grade 3 or 4.
- Related TEAEs.

AESIs will also be tabulated. All AEs will be listed.

9.2.2 Laboratory Data, ECGs, and Vital Signs

Values and changes from baseline in vital signs, quantitative ECG and quantitative laboratory data will be summarized by descriptive statistics by visit. Abnormal values will be summarized by frequency statistics. Frequencies and percentages of subjects with laboratory shifts from induction baseline to the final values according to lab reference ranges (e.g., low, normal, high) will be presented by the respective categories. Subjects with values outside of reference ranges will be listed. Low or high laboratory values will also be flagged in the data listings.

Values and changes from maintenance baseline to each visit in quantitative laboratory and vital sign parameters will be summarized by treatment group.

Qualitative laboratory and ECG results will be summarized by using frequency statistics (e.g., number and percentage of subjects with negative, trace, 1+, 2+, 3+, normal, abnormal clinically significant, or abnormal not clinically significant overall interpretation).

9.3 Efficacy Analysis

All efficacy analyses will be performed on the FAS.

Two sets of analysis specifications for the primary and key secondary endpoints are described due to different regulatory requirements. Section 9.3.1 follows the US FDA guidance and Section 9.3.2 follows the EMA guidance.

9.3.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is clinical remission at Week 8.

The primary estimand (for US/FDA and National Regulatory Authorities other than EMA regulatory purposes) is defined as:

- Population: subjects with moderate to severe active ulcerative colitis who receive at least one dose of study treatment
- Variable: clinical remission
- Intercurrent events (IEs) handling strategy: composite strategy, i.e., subjects will be assigned a known outcome of non-response.
  - [redacted]
  - [redacted]
  - [redacted]
- Population level summary: Proportion of subjects with clinical remission at Week 8 in each treatment group and the difference between treatments.
  - Treatment obefazimod 50 mg or 25 mg QD vs. placebo

The common risk difference in proportions between the treatment groups in the primary efficacy endpoint will be estimated using SAS proc freq and Mantel-Haenszel weights adjusting for inadequate response to advanced therapies (yes/no) and baseline oral CS usage (yes/no). Corresponding two-sided 95% confidence interval (CI) and two-sided nominal p-value will be reported for the difference. Point estimate and corresponding two-sided 95% CI for the odds ratio (OR) will also be presented. Non-responder imputation (NRI) will be applied to subjects with missing data.

[redacted]

The key secondary endpoints evaluated at Week 8 on endoscopic improvement, clinical response, and histologic endoscopic mucosal improvement (HEMI) will be analyzed using the same statistical approach as for the primary endpoint, with estimands defined the same as above, except replacing clinical remission with each of the key secondary outcomes.

[redacted]

[redacted]

9.3.2 Analysis of Co-Primary and Key Secondary Efficacy Endpoints (According to EU/EMA Guidance)

Analysis of Co-Primary Efficacy Endpoints

The primary estimand of the study (for EMA regulatory purposes) is defined as:

- Population: subjects with moderate to severe active ulcerative colitis who receive at least one dose of study treatment
- Variables (co-primary): endoscopic improvement and symptomatic remission
- Intercurrent events handling strategy: composite strategy, i.e., subjects will be assigned a known outcome of non-response:
  - [redacted]
- Population level summary: Proportion of subjects with endoscopic improvement at Week 8 and proportion of subjects with symptomatic remission at Week 8 (co-primary endpoints) in each treatment group and the difference between treatments:
  - Treatment obefazimod 50 mg or 25 mg QD vs. placebo.

The common risk difference in proportions between the treatment groups in each co-primary efficacy endpoint will be estimated using SAS proc freq and Mantel-Haenszel weights adjusting for inadequate response to advanced

therapies (yes/no) and baseline oral CS usage (yes/no). Corresponding two-sided 95% CI and two-sided nominal p-value will be reported for the difference. Point estimate and corresponding two-sided 95% CI for the OR will also be presented. NRI will be applied to subjects with missing data.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Both null hypotheses at a given dose need to be rejected to conclude a statistically significant result for the co-primary endpoints.

The key secondary endpoints evaluated at Week 8 on clinical remission, clinical response, and HEMI will be analyzed using the same statistical approach as for each co-primary endpoint, with estimands defined the same as above, except replacing the endpoint with each of the key secondary outcomes.

Multiplicity Adjustment

The co-primary and ranked secondary efficacy endpoints [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3.3 Analysis of Other Secondary Efficacy Endpoints

All other secondary endpoints will be tested using an exploratory setting. No adjustments for multiplicity will be made among these other secondary endpoints. Nominal two-sided p-values at 5% level will be displayed for all efficacy endpoint treatment comparisons.

Other secondary endpoints include the following categorical endpoints:

- Proportion of subjects in partial clinical response by visit
- Proportion of subjects with an RBS=0 by visit
- Proportion of subjects with an SFS=0 or 1 by visit
- Proportion of subjects with BU = 0 by visit in the subpopulation of subjects with BU at baseline
- Proportion of subjects with FC below 150 µg/g by visit
- Proportion of subjects with histologic improvement per Geboes scoring at Week 8
- Proportion of subjects with endoscopic remission at Week 8
- Proportion of subjects with HEMR per Geboes scoring at Week 8
- Proportion of subjects with histologic remission per Geboes scoring at Week 8
- Proportion of subjects with IBDQ response at Weeks 8
- Proportion of subjects with no more NBM by visit, in the subpopulation of subjects with NBM at baseline
- Proportion of subjects with no EIM at Week 8, in the subpopulation of subjects with EIM at baseline
- Proportion of subjects with symptomatic remission by visit
- Proportion of subjects with UC related visits to the ER, hospitalizations and/or surgery

Categorical endpoints will be analyzed using the same statistical analysis used for the primary endpoint.

In addition, the following continuous endpoints will be analyzed:

- ln-transformed fecal calprotectin by visit
- hs-CRP by visit
- miR-124 expression in rectal/sigmoidal biopsies at Week 8
- miR-124 expression in total blood by visit
- IBDQ scores (including individual IBDQ item under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29) at Weeks 8
- EQ-5D-5L scores by visit
- Fatigue NRS by visit
- FACIT-Fatigue scores at Week 8
- Cytokine concentrations by visit
- MMS at Week 8
- pMMS by visit
- WPAI:UC scores at Weeks 8

Continuous endpoints will be analyzed using the mean change from baseline to the time point at which endpoints are specified for. Efficacy will be evaluated using the Analysis of covariance (ANCOVA) including treatment, and stratification factors of inadequate response to advanced therapies (yes/no) and baseline oral CS usage (yes/no)

as fixed factors, and baseline level of the outcome of interest. Where multiple measurements from the same subject are available, change from baseline may also be analyzed using a mixed model for repeated measures (MMRM). The model will include treatment, visit, treatment-by-visit interaction, inadequate response to advanced therapies (yes/no), baseline oral CS usage (yes/no), baseline value of the continuous outcome of interest, and will include repeated measures within subject using an unstructured covariance matrix.

Results will be presented using the least square means by treatment group and difference between each obefazimod dose group and placebo together with the corresponding 95% confidence intervals. Data will be presented for the observed data in all summary presentations and analyses.

In addition to the PRO scoring methods outlined in Section 5.3.7. e-Diaries entries may also be summarized using the mean of the daily records summarized on a weekly basis for

- stool frequency
- rectal bleeding
- pMMS
- NBM
- BU
- fatigue NRS

Further details will be included in the SAP.

9.4 Determination of Sample Size

9.4.1 Global Study

Sample size calculations are performed with nQuery, version 7 or higher.

Taking into consideration the impact of the strategy to handle intercurrent events, a total of 612 subjects [redacted] This calculation is based on a Chi-square test with a [redacted] and assumes a placebo clinical remission rate [redacted] This sample size also provides [redacted] power to detect the same treatment difference between obefazimod 25 mg and placebo, with the same assumptions, except using a type I [redacted] (according to the multiplicity adjustment procedure). This sample size will also allow the detection of a difference of at least [redacted] in the clinical remission rate at Week 8 among subjects with inadequate response to advanced therapies (assuming [redacted] between obefazimod 50 mg and placebo with a statistical power of at least [redacted] Differences of [redacted] and [redacted] were also evaluated, and the associated powers are [redacted] and [redacted] respectively. These calculations are based on a Chi-square test [redacted] (two-sided) and assumes a placebo clinical remission rate of [redacted]

Additional Sample Size Calculation for the Co-primary Endpoints (According to the EU/EMA Guidance)

A statistical power calculation for co-primary endpoints according to EU/EMA guidance is also performed. The calculation for each of the co-primary endpoints is based on a Chi-square test with a [redacted]

Symptomatic remission:

A total of 612 subjects [redacted] will provide [redacted] power to detect a [redacted] difference between obefazimod 50 mg and placebo in the symptomatic remission rate at Week 8, assuming a placebo rate [redacted] and a [redacted] This sample size also provides [redacted] power to detect the same treatment difference between obefazimod 25 mg and placebo, with the same assumptions, except using a [redacted] (according to the multiplicity adjustment procedure).

Endoscopic improvement:

A total of 612 subjects [redacted] will provide [redacted] power to detect a [redacted] between obefazimod 50 mg and placebo in the endoscopic improvement rate at Week 8, assuming a placebo rate of [redacted] and a [redacted] This sample size also provides at least [redacted] power to detect the same treatment difference between obefazimod 25 mg and placebo, with the same assumptions, except using a [redacted] (according to the multiplicity adjustment procedure).

Considering the clinical hypotheses described above for the co-primary endpoints of endoscopic improvement and symptomatic remission, the statistical power to detect the clinically relevant differences for both co-primary endpoints is [redacted] for the comparison between obefazimod 50 mg and placebo and [redacted] for the comparison between obefazimod 25 mg and placebo.

This calculation assumes that there is no correlation between endoscopic improvement and symptomatic remission. The statistical power will be even higher considering these two outcomes are likely positively correlated.

9.4.2 [redacted]

[redacted]

9.5 Interim Analysis

No interim analysis is planned.

9.6 PK Analysis

Plasma concentrations of obefazimod [redacted] will be assessed from samples collected at specified pre- and post-dose sampling times on D1, D28 and D56 as follows:

- for group 1: pre-dose, 0.5, 1.5, 3 h (and 6 h and/or 10 h if possible) post-dose
- for group 2: pre-dose, 1, 2, 4 h (and 8 h and/or 12 h if possible) post-dose

A descriptive summary of observed plasma concentrations will be displayed by time and by treatment group.

In addition, the PK data will be incorporated into the global population model by adding the concentrations of obefazimod [redacted] collected during the current study to the existing model to characterize the PK of both compounds in the target population. A separate population PK analysis report that includes data from all Phase 3 induction and maintenance (to Week 44) studies will be written separately.

Full details of PK analysis will be provided in the PK SAP.

9.7 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

10 Regulatory and Ethical Consideration for the Study Conduct

10.1 General Requirements

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

- International Council for Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6).
- US 21 Code of Federal Regulations (CFR) dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards IMPs for human use, as well as the requirements for authorization of the manufacturing or importation of such products.
- Declaration of Helsinki and its amendments.
- EudraLex GMP guidelines Annex 13 related to shipment, storage and handling of investigational products.
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
- Regulation (EU) 536/2014 of the European Parliament and of council, which introduces the Clinical Trials Information System (CTIS) that harmonizes the submission, assessment, and supervision processes for clinical trials throughout the EU and EEA.

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 GCP to which it conforms.

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

Although in vitro studies do not indicate ethnic differences in response to obefazimod as stated in the Investigator Brochure, the collection of race and ethnicity data in this trial may also help identify any potential difference in pathophysiology (including environmental or social factors contributing to ulcerative colitis. Where allowed in local law, race and ethnicity data will be collected from subjects to facilitate the assessment of the safety and efficacy of obefazimod by demographic subgroups (FDA Guidance, Ulcerative Colitis; ICH Guidance E5, Ethnic Factors in the Acceptability of Foreign Clinical Data). The data regarding race and ethnic origin will be available only in the form of total numbers and no individual will be identifiable from the statistics. Subjects must provide their consent to the collection of race and ethnicity data collection.

The Sponsor, or its representative, will obtain favorable opinion/approval to conduct the study from the appropriate regulatory authorities in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

10.2 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study and upon each substantial modification, the study protocol, and amendments if applicable as well as other appropriate study-related documents will be submitted to an independent IRB or IEC, respectively.

For the EU and EEA countries, as per the EU Regulation (EU) 536/2014, the ethical review shall be performed by an IEC in accordance with the law of the Member State concerned. The review by the IEC may encompass aspects addressed in Part I of the assessment report for the authorization of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned.

For other countries, the procedures regarding IEC or IRB shall follow the applicable laws and regulations.

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.

10.3 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 informed consent collection procedure will be duly documented in the subject medical chart.

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements.

A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record.

Recruiting adolescent subjects is allowed provided it has been approved by the relevant Regulatory Authority and IEC-IRB for study ABX464-105, and they are at least 16 years old at the time of the informed consent and/or assent signature. Recruiting adolescents is currently not approved in the EU/EEA and Ukraine.

In the current study, subjects will be asked to sign the core study ICF, and wherever applicable the General Data Protection Regulation related ICF [redacted]

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.

Paper ICF or an electronic ICF are the format that will be used for this study. In the case of the latter, subjects will e-sign directly on the electronic device. An electronic version will be sent be e-mail to the subjects and may be printed upon request.

10.4 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 Site File.

In addition, due to the cumbersome procedures related to the study (e.g., 4 to 5 on-site visits, 2 endoscopies, lab samplings) subjects could be financially compensated by the Sponsor in accordance with the national regulations and the approval of the IECs.

11 Study Management

11.1 Source Documents

Source documents are defined as original documents, data and records. This may include but is not limited to hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing, recorded data from automated instruments, images (regardless of the support) and related reports, photographic negatives.

Data collected during this study must be recorded to the appropriate source document.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents. In the case of unexpected situations, such as an ongoing pandemic or other major emergencies, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study sites.

11.2 Electronic Data Entry

Electronic Data Capture (EDC) will be used to record data required by the protocol. Electronic Case Report Forms (eCRF) will be used for data collection via a computer at the investigational site.

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

The EDC system used for this study is called [redacted] The EDC system and the study-specific eCRFs comply with the current GCP ICH E6 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, site data entry staff, Sponsor staff and CRO staff, including project managers, CRAs and data managers).

Support is available to help all users with this tool including eCRF Data Completion Guidelines and EDC helpdesk (support line).

All subject data will be entered in the eCRF through transcription from source documents or through system integration from subject entered e-Diaries.

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 CRA’s disposal for review.

11.3 ePRO

Subject reported data must be completed for all screened/enrolled subjects in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) system.

The ePRO system will comply with the GCP ICH E6 requirements, European and FDA (21 CFR Part 11) regulations. The documentation related to the system validation of the ePRO system is available through the vendor.

11.4 Data Management

Data management will be outsourced to a CRO. The data managers will issue electronic data queries 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.

11.5 Data Coding

AEs, concomitant diseases, medical/surgical histories will be coded using MedDRA.

Prior and concomitant medication will be coded using the WHO-Drug dictionary.

11.6 Randomization

All subjects will be centrally randomized using an Interactive web-based Response System (IWRS). The allocation will be done using the minimization method, which will be described in detail in a separate Randomization Requirements Specification (RRS), plan/document.

At screening, all subjects will be assigned a unique identification number by the IWRS. Eligible subjects as defined in Sections 4.3.1 and 4.3.2 will be centrally randomized in a 1:1:2 ratio to receive either placebo, obefazimod 25 mg, or obefazimod 50 mg QD in a double-blind manner. The randomization will be stratified according to the following factors:

- Subjects with inadequate response to advanced therapies (lack of response, loss of response or intolerance to advanced therapies) (Yes/No)
- Subjects with concomitant oral CS usage at baseline (Yes/No)

The IWRS will assign a randomization number that will encode the subject's treatment group assignment according to the randomization list generated by the Clinical Supply Chain Management Department of the CRO contracted for the study. This information will be provided to the site by the IWRS system.

11.7 Study Monitoring

The study will be conducted in accordance with current ICH E6 GCP guidelines. The appointed monitor will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and the Sponsor 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 the current ICH E6 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. The investigator must also ensure provision of sufficient time, space, and qualified personnel for the monitoring visits.

In the case of unexpected situations, such as an ongoing pandemic or other major emergencies, on-site monitoring visits might be postponed and delayed due to national contingency measures. Remote monitoring will be preferred during this period.

11.8 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.

The Sponsor 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 current ICH E6 requirements, any institutional requirements or local laws and regulations, or the Sponsor standards/procedures; otherwise, by default the retention period will be 25 years.

The investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or 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.

11.9 Quality Assurance and Inspection by Authorities

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct quality assurance audits. Regulatory authorities may also conduct regulatory inspections 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 regulatory inspections and audits. If an audit or inspection occurs, the investigator and institution will allow the auditor/inspector direct access to all relevant documents and electronic systems (i.e., electronic medical records) 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.
- ICFs of the subjects.
- Approved study protocol and amendments and investigator brochure.
- Study plans and manuals such as the pharmacy manual, IWRS manual and laboratory manual.
- Treatment accountability.
- Safety reporting.
- Study site file.
- Study personnel.
- Log of monitoring visits and monitoring process.
- Eligibility review.
- Subject disposition.
- Assessment of protocol compliance.
- Reporting of protocol deviations.
- Documentation of adverse events and concomitant medications.
- E-compliance of systems and digital signatures.
- Medical records and other source documents.
- Site facilities.
- Reports to the IRB/IEC and the sponsor.
- Record retention.

11.10 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.

The Sponsor 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 significant 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 and relevant IRB/IECs will also be informed by the sponsor 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 the Sponsor procedures. All data must be returned to the Sponsor. Arrangements will be made for any unused investigational product based on the relevant Sponsor procedures for the study.

11.11 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, the Sponsor 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 coordinated by the sponsor and will include the primary and key secondary efficacy endpoints and a summary of safety including all data from participating sites. Secondary publications will also be coordinated by the sponsor (abstracts, presentations, manuscripts etc.) and will reference the original publication. Authorship will be determined based on the international consortium of medical journal editors (ICMJE) criteria for authorship and will be based on overall contributions to the design, data collection, and analysis of the data. Note that the Sponsor is entitled to delay any proposed secondary publication, in order to obtain patent protection, if required.

11.12 Ownership and Confidentiality

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

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 the Sponsor 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.

11.13 Data Protection

Study's records are processed in accordance with the applicable regulations in particular with Electronic Records and Electronic Signatures (ER/ES) which includes at least FDA 21 CFR Part 11, EMA Guideline on Computerised Systems and Electronic Data in Clinical Trials and EUDRALEX Volume 4 Annex 11, to guarantee data integrity remaining through the computerized systems processing, collecting, storing, managing, transferring and archiving the study records from end-to-end perspectives (i.e., full study dataflow).

The logical and physical technical measures are set in place to address strict confidentiality and integrity of study data throughout the trial and include, but are not limited to the following:

- User access limited to authorized users only (e.g., access control management with User ID & password plus Multi-Factor Authentication where appropriate, user access management procedure

including periodic access reviews, segregation of duties, audit trail & traceability, backups and recovery plan).

- Encryption methodologies and other security measures to support data transfer/in transit as well as data storage (e.g., servers securities to prevent logical and physical disasters with firewalls, antivirus, troubleshooting, maintenance of hardware, monitoring of networking, monitoring of incidents where applicable, security policies, business continuity and disaster recovery plans).

In addition, subject's personal data shall be treated according to the Sponsor's Privacy Policy in compliance with European and local applicable laws and regulations especially by using pseudonymization throughout the data life cycle.

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[redacted]

13 Appendices

13.1 Appendix 1: Prohibited Medication belonging to the categories of [redacted]

Prohibited medications belonging to the categories of [redacted] are detailed below.

For the full list of prohibited medications and procedures, see Section 4.4.2

[redacted] (prohibited concomitant medications)

[redacted]

[redacted] (prohibited concomitant medications)

[redacted]

[redacted] (prohibited concomitant medications)

[redacted]

[redacted] (prohibited concomitant medications)

[redacted]

13.2 Appendix 2: Modified Mayo Score (MMS) and Partial Modified Mayo Score (pMMS)

The Total MS evaluates UC stage, based on four parameters: stool frequency, rectal bleeding, endoscopic evaluation and Physician's global assessment. Each parameter of the score ranges from zero (normal or inactive disease) to 3 (severe activity). The following table indicates, for each parameter, the input values with their respective scores.

Parameter	Clinical evaluation (single choice)	Score
1. Stool frequency (per day)	normal number of stools	0
	1-2 more than normal	1
	3-4 more than normal	2
	≥ 5 more than normal	3
2. Rectal bleeding (indicate the most severe bleeding of the day)	No blood seen	0
	Stool with streaks of blood	1
	Stool with more than streaks of blood	2
	Blood alone passed	3
3. Endoscopy	Normal appearance of mucosa	0
	Mild disease (erythema, decreased vascular pattern), no friability	1
	Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)	2
	Severe disease (spontaneous bleeding, ulcerations)	3
4. Physician's global assessment	Normal	0
	Mild disease	1
	Moderate disease	2
	Severe disease	3

Calculation formula for the Total Mayo Score: sum of the scores of the four parameters.

The Modified Mayo Score (MMS) or 3-componant Mayo score uses the following three components of the Total MS: stool frequency, rectal bleeding and Mayo endoscopic subscores.

The partial Modified Mayo score (pMMS) uses the non-invasive components of the MMS: Stool Frequency and Rectal Bleeding subscores, excluding the score for the endoscopic findings. The pMMS maintains a good relationship with the Modified Mayo Score in identifying clinical response as perceived by subjects. It considers the clinical parameters, each of which is assigned a score from 0 to 3 according to the clinical evaluation.

13.3 Appendix 3: Inflammatory Bowel Disease Questionnaire (IBDQ)

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

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from
   - 1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
   - 2 EXTREMELY FREQUENT
   - 3 VERY FREQUENT
   - 4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
   - 5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
   - 6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
   - 7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from
   - 1 ALL OF THE TIME
   - 2 MOST OF THE TIME
   - 3 A GOOD BIT OF THE TIME
   - 4 SOME OF THE TIME
   - 5 A LITTLE OF THE TIME
   - 6 HARDLY ANY OF THE TIME
   - 7 NONE OF THE TIME
3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from
   - 1 ALL OF THE TIME
   - 2 MOST OF THE TIME
   - 3 A GOOD BIT OF THE TIME
   - 4 SOME OF THE TIME
   - 5 A LITTLE OF THE TIME
   - 6 HARDLY ANY OF THE TIME
   - 7 NONE OF THE TIME
4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from
   - 1 ALL OF THE TIME
   - 2 MOST OF THE TIME
   - 3 A GOOD BIT OF THE TIME
   - 4 SOME OF THE TIME
   - 5 A LITTLE OF THE TIME
   - 6 HARDLY ANY OF THE TIME
   - 7 NONE OF THE TIME
5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from
   - 1 ALL OF THE TIME
   - 2 MOST OF THE TIME
   - 3 A GOOD BIT OF THE TIME
   - 4 SOME OF THE TIME
   - 5 A LITTLE OF THE TIME
   - 6 HARDLY ANY OF THE TIME
   - 7 NONE OF THE TIME
6. How much energy have you had during the last 2 weeks? Please choose an option from
   - 1 NO ENERGY AT ALL
   - 2 VERY LITTLE ENERGY
   - 3 A LITTLE ENERGY
   - 4 SOME ENERGY

5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from
1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please

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

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from
1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from
1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many subjects with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from
1 ALL OF THE TIME

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

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from
1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME

6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from
1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from
1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

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

13.4 Appendix 4: EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES (e.g., work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN/DISCOMFORT

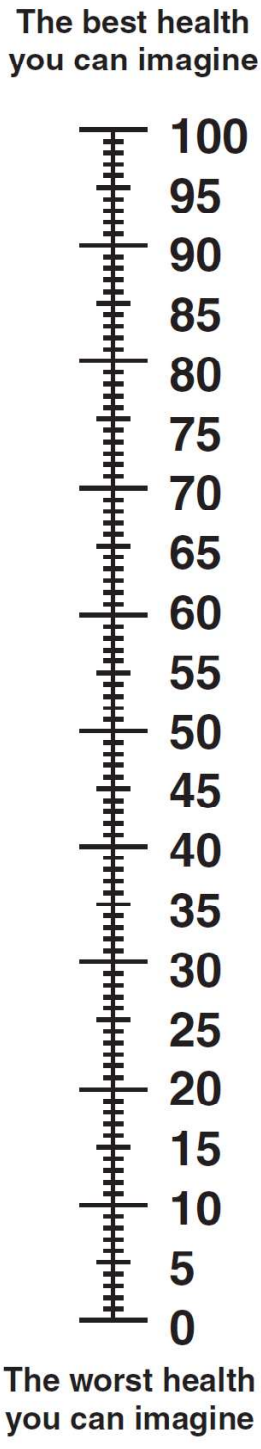
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY/DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am very anxious or depressed ❑
- I am extremely anxious or depressed ❑

1. We like to know how is your health today.
2. This scale is marked from 0 to 100.
3. 100 means the best health you can imagine.
   0 means the worst health you can imagine.
4. Mark an X on the scale to indicate how is your health today.
5. Now, please note the number you marked on the scale in the box below.

Your Health Today = ☐



13.5 Appendix 5: Work Productivity and Activity Impairment Questionnaire

Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis V2.0 (WPAI:UC)

The following questions ask about the effect of your ulcerative colitis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO _____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your ulcerative colitis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your ulcerative colitis. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your ulcerative colitis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If ulcerative colitis affected your work only a little, select a low number. Select a high number if ulcerative colitis affected your work a great deal.

   Consider only how much ulcerative colitis affected productivity while you were working.

Ulcerative colitis had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Ulcerative colitis completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your ulcerative colitis affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If ulcerative colitis affected your activities only a little, select a low number. Select a high number if ulcerative colitis affected your activities a great deal.

   Consider only how much ulcerative colitis affected your ability to do your regular daily activities, other than work at a job.

Ulcerative colitis had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Ulcerative colitis completely prevented me from doing my daily activities

   CIRCLE A NUMBER

13.6 Appendix 6: FACIT-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

[redacted]