STATISTICAL ANALYSIS PLAN

ABX464-104

A phase 2b, open-label, efficacy, and safety study of ABX464 as maintenance therapy in patients with moderate to severe Ulcerative Colitis

AUTHOR: LYNDA OLINGER, GANESH L

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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	Name	Signature	Date
Author:	Ganesh L		
Position:	Manager, Biostatistics		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Josianne Nitcheu		
Position:	Project Coordinator		
Company:	Abivax		
Approved By:	Paul Gineste		
Position:	Vice President, Clinical Operations		
Company:	Abivax		

MODIFICATION HISTORY

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0.2	24 February 2022	Ganesh L	Revised based on amended protocol 4.1.0 specifically for interim analysis.
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0.4	28 Oct 2022	Ganesh L	Updated as per Protocol amendment version 5.1
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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Theoretical Chemical
β-hCG	Beta human chorionic gonadotropin
BLQ	below the lower limit of quantification
BMI	Body Mass Index
BOLS	baseline of the open label study
bpm	beats per minute
CI	Confidence Interval
CM	concomitant medicine
CONS	All Subjects Consented Analysis Set
CRT	Core Review Team
CRP	C-Reactive Protein
CS	clinically significant
CTC-AE	Common Terminology Criteria for Adverse Events, version 4.0
CTMS	Clinical Trial Management System
DA	drug accountability
DBL	database lock
DBP	Diastolic Blood Pressure
DHD	data handling database
DM	Demography
DOV	day of visit
DR	data review
DSMB	Data and Safety Monitoring Board
DTL	data team lead
EC	Exposure
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	end of study
FAS	Full Analysis Set
GLDH	glutamate dehydrogenase
HR	heart rate
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ISB	induction study baseline
LDH	lactate dehydrogenase
LLT	lower level term
LOCF	Last Observation Carried Forward
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MH	medical history

Min	minimum
miR	micro-RNA
mL	milliliter
mmHg	millimeters of mercury
MMS	Modified Mayo Score
msec	millisecond
MW	medical writing
NCS	not clinically significant
o.d.	Once Daily
PD	pharmacodynamics
PD	protocol deviation
PK	pharmacokinetics
PL	project lead
pMMS	Partial Modified Mayo Score
PPAS	Per Protocol Analysis Set
PR	procedure history
PREG	pregnancy test
PT	Preferred Term
QA	quality assurance
QC	quality control
QoL	Quality of Life
RHI	Robarts Histopathology Index
RNA	ribonucleic acid
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
STL	Statistics team lead
TEAE	treatment emergent adverse event
TMS	Total Mayo Score
TNF	Tumor Necrosis Factor
TSH	Thyroid Stimulating Hormone
UC	Ulcerative Colitis
UCHX	Ulcerative colitis history
ULN	Upper Limit Normal
ULQ	upper limit of quantification
WHO	World Health Organization

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol ABX464-104. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 5.1, dated 11 July 2022.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to assess in all patients the long-term efficacy of ABX464 given at 50 mg once daily (QD) on clinical remission at Week 48 compared to the induction study (ABX464 -103) baseline (ISB).

2.2. Secondary Objectives

For all secondary objectives, baseline of the open label study (BOLS) will be Week 16 of the induction study, or Week 8 of the induction study if no endoscopy results are available for Week 16.
The secondary objectives are:

- To evaluate clinical remission at Week 48 compared to BOLS
- To evaluate the effect of ABX464 50mg QD on:
    - Modified Mayo Score (MMS) at Week 48 and Week 96 and on partial Modified Mayo Score (pMMS), among all patients at every study visit compared to ISB
    - Endoscopic improvement and remission and sustained endoscopic improvement and remission, by segment, at Week 48 compared to ISB and BOLS
    - Stool and rectal bleeding frequency at every study visit compared to BOLS
    - Proportion of patients with Glucocorticoid-free Clinical Remission at Week 48

- Fecal calprotectin and C-reactive Protein (CRP) levels at Week 24, Week 48, Week 60, Week 72, Week 84, and Week 96 visits compared to BOLS
- Clinical response at Week 48 compared to ISB and BOLS
- miR-124 expression in colon tissue (Ribonucleic Acid [RNA] later) at Week 48 and in total blood at Week 24, Week 48, and Week 96
- Rectal/sigmoidal infiltrates using the Robarts Histopathology Index (RHI), Geboes and Nancy Histology Scoring Scales at Week 48 compared to ISB and BOLS
- Patient's quality of Life (QoL) measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 24 and Week 48 compared to BOLS

- To evaluate the long-term safety profile of ABX 464 50 mg QD
- Echocardiography objective: To evaluate the effect of ABX464 on cardiac function as assessed through echocardiograms.

2.3. Estimands

The primary, and secondary estimands to support regulatory decisions are described in Table A below. The intercurrent event is the early discontinuation of patients from the study and/or missing Week 48 efficacy assessments.

Table A: List of Estimands

Estimand	Definition	Attributes			
		Population	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
Primary	Long term efficacy of ABX464 50 mg dose on clinical	All patients randomized, received at least one dose of study	Clinical remission achieved at Week 48 compared to	Patients with missing Week 48 assessment including discontinued patients will be considered to not have achieved clinical remission	Proportion of patients achieving clinical remission

	remission at Week 48	drug and provided at least one efficacy data point	ISB		
Secondary	The effect of ABX464 50 mg dose on secondary variables	All patients randomized, received at least one dose of study drug and provided at least one efficacy data point	Clinical Response, Endoscopic improvement, and Endoscopic remission at Week 48	Patients with missing Week 48 assessment including discontinued patients will be considered as non-responders	Proportion of patients achieving Clinical Response, Endoscopic improvement, and Endoscopic remission
Secondary	The effect of ABX464 50 mg dose on secondary variables	All patients randomized, received at least one dose of study drug and provided at least one efficacy data point	Clinical Remission, Clinical Response, Endoscopic improvement, and Endoscopic remission at Week 96	Patients discontinued prior to Week 96 are considered as non-responders. LOCF method is used to impute completers (not discontinued). The value will be carried forward from Week 48.	Proportion of patients achieving Clinical Remission, Response, Endoscopic improvement, and Endoscopic remission
Secondary	The effect of ABX464 50 mg dose on secondary variables	All patients randomized, received at least one dose of study drug and provided at least one efficacy data point	Mean change from ISB to Week 48 in pMMS, MMS, stool frequency and rectal bleeding sub scores	Missing pMMS components (stool frequency and rectal bleeding sub scores) and endoscopy scores at Week 48, pMMS and MMS will not be imputed.	Mean change from ISB
			Mean change from baseline to	Missing Fecal calprotectin and CRP values will not be imputed.	Mean change from baseline

			Week 48 in Fecal calprotectin and CRP levels		

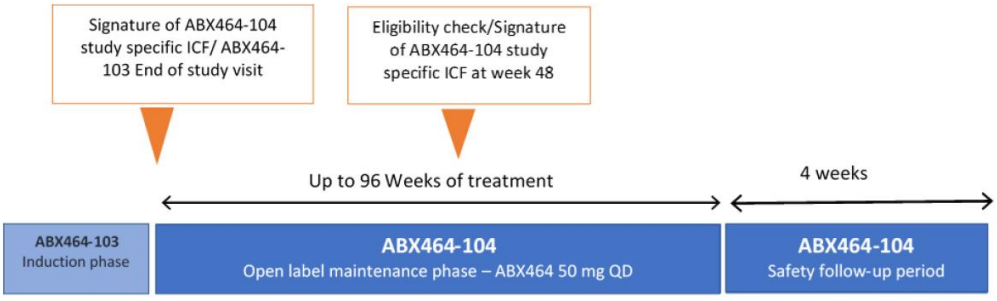
3. STUDY DESIGN

3.1. General Description

This study is an open-label study to evaluate the long-term safety and efficacy profile of ABX464 50 mg QD in patients with moderate to severe ulcerative colitis (UC) who have been previously enrolled in the ABX464-103 clinical study (induction study) and who are willing to continue their treatment with ABX464 as long-term (maintenance) remission therapy. All patients who have completed the 16-week (± 4 days) induction treatment period (ABX464-103) will be eligible for this maintenance study regardless of their clinical response and will receive 1 capsule of ABX464 50 mg once daily during up to 96 weeks providing the patient has a clinical response at week 48. Patients will be treated for a maximum of 96 weeks in this maintenance study. After the treatment period, patients will be followed for 4 more weeks for safety purposes.

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

The study design is presented below:



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

In the event of clinical progression of the disease during the open-label maintenance phase, defined as at least a 2-

point increase from the baseline partial Modified Mayo Score (pMMS) with a pMMS ≥ 4 confirmed by an endoscopy sub-score of 2 points or higher, the patient will be withdrawn from the study.

3.2. Schedule of Events

Schedule of events can be found in Section 5.1 of the protocol.

3.3. Changes to Analysis from Protocol

Analyses of infiltrate/histopathology and miRNA-124 levels in blood and tissue will be analysed and reported separately by an independent vendor and will be excluded from the final outputs and analysis conducted by IQVIA.

The analysis of the following secondary endpoints will not be addressed in this SAP:

- Change relative to baseline in miRNA-124 expression in rectal/sigmoidal biopsies at Week 48 and Week 96 and in total blood at Week 24, Week 48, and Week 96
- Reduction relative to ISB of infiltrate/histopathology (rectal/sigmoidal biopsies) using RHI, the Geboes and Nancy Histology Scoring Scale at Week 48

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Data Safety Monitoring Board (DMSB) meetings
- Interim Analysis
- Final Analysis

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

A DSMB will review the safety of the trial during the entire study period. A DSMB charter describing the methodology and presentation of results and access to results will be provided by Abivax as a separate

document.

The ICVSC will be responsible for an on-going evaluation of cardiac adverse events of special interest (Cardiac AESIs), for treatment emergent echocardiographic findings, and for treatment emergent changes of cardiac safety biomarkers (as detailed above). The ICVSC will review cardiac adverse events on an on-going basis.

4.2. Interim Analysis

An interim analysis will be performed when all the patients have completed the Week 48 visit for SAF and FAS. The interim analysis will summarize efficacy and safety data descriptively for the following:

- Reduction relative to ISB and BOLS in Modified Mayo Score and in partial Modified Mayo Score at every study visit till Week 48
- Mean change in Stool Frequency, and Rectal Bleeding Score from BOLS to Week 48
- Proportion of patients with Clinical remission/response and Endoscopic remission /improvement at Week 48 will be summarized for the following categories as well
    a) With/without clinical remission/response or endoscopic remission/improvement at the BOLS
    b) Induction study arms (100 mg, 50 mg, 25 mg, Placebo)
    c) With/without Previous Biologics/JAK exposure
    d) Sustained clinical remission/response and endoscopic remission/improvement: Sustained remission/response/improvement at Week 48 from Week 8 and Week 16 of Induction Study.
    e) Glucocorticoid free (at least 8 weeks) clinical remission (not applicable for Endoscopic remission/improvement)
    f) Loss of clinical remission/response and endoscopic remission/improvement: Lost remission/response/improvement at Week 48 compared to Week 8 and Week 16 of the Induction Study.
    g) Newly clinical response/remission and endoscopic remission/response: New remission/response/improvement at Week 48 compared to Week 8 and Week 16 of the Induction Study.

- Fecal calprotectin results: Along with the descriptive statistics of actual values and change from baseline, percentage of patients with FCP level <50µg/g, <150µg/g, <250µg/g, and < Median will be presented for each visit.
- Safety parameters
- Hematology and biochemistry parameters: Clinically significant abnormalities will be listed and summarized.

4.3. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Abivax Authorization of this SAP, Abivax Authorization of Analysis Sets and Database Lock (DBL).

5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to DBL. To facilitate this, a Data Review (DR) process will be co-ordinated by the IQVIA Statistical Team Lead (STL).

5.1. Process for Analysis Set Assignment

A data review meeting will be conducted prior to the Database Lock, to review Critical/Major protocol deviations referencing the Blind Data Review plan of Induction study, along with the exclusion reasons mentioned below in section 5.5. Analysis of assignment spreadsheet will be authorized by sponsor before Database lock and incorporated in the final analysis.

5.2. All Patients Consented Analysis Set [CONS]

The All Patients Consented (CONS) Analysis Set will contain all patients who provided written informed consent (IC) to the Open label study.

The following patients will be excluded from this Analysis Set:

- Patients who did not provide written informed consent at the BOLS visit

5.3. Safety Analysis Set [SAF]

The Safety Analysis Set (SAF) will include all patients who have received at least one dose of the study medication. If there is any doubt as to whether a patient was treated or not, it will be assumed that the patient was treated for the purposes of analysis. The SAF will be used for all safety analyses.

The following patients will be excluded from this Analysis Set:

- All patients excluded from the CONS Analysis Set
    - Patients who have not received at least one dose of the study medication:

5.4. Full Analysis Set [FAS]

The Full Analysis Set (FAS) will include all patients included in the study who have received at least one dose of the study medication, and who have BOLS data for at least one efficacy variable.

The following patients will be excluded from this Analysis Set:

- All patients excluded from the SAF
- All patients who do not have baseline data for at least one efficacy variable

5.5. Per Protocol Analysis Set [PPAS]

The Per Protocol Analysis Set (PPAS) will include all patients in the FAS who do not have critical/major PDs that would affect the evaluation of the primary efficacy endpoint. From a statistical analysis

perspective, the reason(s) for exclusion of patients from the PPAS may be a PD or other factors affecting the primary efficacy outcome. PDs identified during the clinical conduct of the study, as authorized in the final PD log, will also be taken into consideration in the final assignment of patients to the analysis sets.

Reasons for exclusion include:

- Insufficient essential efficacy data i.e. no MMS score or its components at Week 48
- Non-compliance with the inclusion or exclusion criteria, including completing procedures as per protocol
- Non-compliance with the study medication up to Week 48 (Compliance < 80%)
- Intake of prohibited medication up to Week 48
- Non-compliance with time window up to Week 48 (+/- 7 days) (to be confirmed at Data Review meeting)
- Induction Study Per Protocol definition not met, i.e. excluded from per protocol based on Induction Study Blind Data Review meeting.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of maintenance study medication and is Day 1 of the maintenance study. Patients will take the first dose of ABX464-104 medication the day after Day 113 of the induction study.

- If the date of the event is on or after the reference start date, then:

  Study Day = (date of event – reference start date) + 1

- If the date of the event is prior to the reference start date, then:

  Study Day = (date of event – reference start date)

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear missing in the listings.

6.2. Baseline

ISB (Induction Study Baseline) is the baseline measurement for the Induction (ABX464-103) study.
BOLS (Baseline of Open Label Study) is the Day 113 (Week 16) measurement of the Induction (ABX464-103) study. Week 48 is considered as baseline for Echocardiography parameters.
In the case where the last non-missing measurement and the reference start date coincide, such measurement will be considered as the baseline measurement, but adverse events (AEs) and concomitant medications commencing on the reference start date will be considered post-baseline.

6.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the best/worst case value where required (example: shift table). In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries.

Early discontinuation data will be mapped to the next available visit number for by-visit summaries. Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. Windowing Conventions

There will be no visit windowing applied in this study.

6.5. Statistical Tests

Only descriptive analyses of safety and efficacy variables will be conducted in this study.

6.6. Common Calculations

For quantitative measurements,

- Change from baseline of the open label study (BOLS) = Test Value at Visit X – Open Label (Maintenance) Study Baseline Value

Open label study baseline value will be determined at Week 16 (Day 113) of the induction study for all variables except MMS, which can be determined at Week 8 (Day 57) of the induction study if no Week 16 data are available.

- Change from induction study baseline (ISB) = Test Value at Visit X – Induction Study Baseline Value

A patient will be considered to have a reduction relative to baseline (ISB or BOLS) in variable X at Visit X when change from the respective baseline for variable X is less than zero.

6.7. Software Version

All derivations, statistical analyses, summaries, and listings will be generated using SAS® version 9.4 or higher (SAS® Institute, Inc., Cary, North Carolina). Graphics will be prepared using the same versionof SAS®.

6.8. Statistical Considerations

Summaries will include descriptive statistics for continuous variables (sample size [n], mean, standard deviation [SD], standard error of the mean [SEM], median, minimum and maximum) and for categorical variables (frequency [n] and percentage). SEM will only be determined for laboratory, vital signs, and ECG assessments. Percentages will be based on the number of patients within the relevant analysis set, or the number of patients with data available where relevant (e.g. shift tables). Proportions will be expressed as percentages.

If the original data has N decimal places, then the summary statistics will have the following decimal places:

Minimum and maximum: N

Mean, median, confidence intervals, ratios: N + 1

SD, SEM: N + 2

Percentages will be reported to one decimal place.

6.9. Multicenter Studies

This study will be conducted by multiple investigators at multiple centres internationally. As only descriptive statistics will be determined for this study, there will be no pooling of data with other

countries or into regions (example: Western Europe, Eastern Europe).

6.10. Missing Data

Analysis of missing primary and secondary efficacy data is explained in sections **Error! Reference source not found.** and **Error! Reference source not found.**. Missing safety data will not be imputed. Percentages based on the number of patients with data available will not take missing observations into account.

6.11. Multiple Comparisons/ Multiplicity

No adjustment for multiple comparisons is needed, as only descriptive statistics will be presented.

6.12. Examination of Subgroups

Subgroup analyses will be conducted as stated in the relevant analysis sections.
The following subgroups will be assessed for the primary efficacy variable, the proportion of patients with clinical remission at Week 48, and secondary efficacy variables, MMS and pMMS:

- Patient efficacy status at the end of the induction study (Week 16)
    - Remitter (patients with clinical remission)
    - Responder/non-responder (patients with/without clinical response)
- Treatment received during the induction phase
    - ABX464 25 mg
    - ABX464 50 mg
    - ABX464 100 mg
    - Placebo

7. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs. The templates provided with this

SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

8. DISPOSITION, WITHDRAWALS AND PROTOCOL DEVIATIONS

All patients who provide informed consent will be accounted for in this study. The number of patients who are baseline failures and the reasons for failure will be presented. A patient is a baseline failure if the patient signs informed consent but withdraws before first dosing in the maintenance phase. The number and percentage of consented patients and included in each of the analysis sets, as well as reasons for exclusion from each of the analysis sets, will be presented. In addition, the number and percentage of discontinued patients with their reason for discontinuation will be presented.

Listings will include completion or early discontinuation, and the reason for early discontinuation for each patient, as well as details of protocol deviations, inclusion/exclusion criteria and analysis sets..

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the CONS, FAS, and PPAS. Age (years), age categories (<30 years, 30 to < 60 years, >= 60 years), country, gender, child-bearing potential, baseline weight and BMI (BOLS) and baseline height (ISB) will be reported for this study. MMS (BOLS) will be presented descriptively and in categories of scores 0 to 4, 5 to 6 and 7 to 9. Patient status at the end of the induction study, treatment received during the induction study, corticosteroid usage, and previous exposure to biologics/JAK inhibitors will also be presented. No statistical testing will be carried out for demographic or other baseline characteristics.

9.1. Derivations

$$BMI = \frac{Weight\ (kg)}{\{Height\ (m)^{2}\}}$$

9.2. Medical and Procedure History

Medical and Procedure History information will be listed for the SAF analysis set. Conditions or procedures which stop prior to the BOLS visit will be recorded as Medical and Procedure History. Any other medical condition or procedure occurring on or after BOLS will be recorded as an AE.

Medical and Procedure History will be coded using version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA) (latest). Data captured on the Medical and Procedure History pages of the eCRF will be listed by patient and will include System Organ Class (SOC) and Preferred Term (PT) coding.

10. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be listed by the Anatomical Therapeutic Chemical (ATC) Level 2

and PT for the SAF and coded using the latest version of the World Health Organization (WHO) Drug Dictionary. Prior and concomitant medications will be listed, without time limit for medications used to treat UC, and medications used prior to the start of the study or during the study for all other medications.

- 'Prior' medications are medications which started and stopped prior to the first dose of maintenance study medication.
- 'Concomitant' medications are medications which started prior to, on or after the first dose of maintenance study medication, but before the last dose of maintenance study medication, and ended on or after the date of first dose of maintenance study medication or were ongoing at the end of the study.

See **Error! Reference source not found.** for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case, i.e. concomitant.

11. STUDY MEDICATION EXPOSURE

Exposure to study medication in days and the total number of daily doses taken during the study will be summarized for the FAS.
The dates of first study medication administration and last study medication administration will be obtained from the eCRF Exposure form (EC).

11.1. Derivations

- Overall duration of study medication exposure (days) = Stop date of last study medication administration – Start date of first study medication administration + 1.

- Duration of study medication exposure (days) at Visit X measures the treatment duration from Visit X to Visit X+1 and is calculated as follows:

Duration of study medication exposure (days) at Visit X = (Stop date of study medication issued at Visit X) – (Start date of study medication issued at Visit X) +1

12. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be presented for the FAS

Overall compliance with study medication will be calculated as the number of capsules taken (total dispensed – total returned) divided by the expected number of capsules expressed as a percentage.

Patients will take 1 capsule daily from Day 1 to the end of treatment and will receive 30 capsules at each dosing visit. The number of capsules dispensed and returned will be obtained from the Drug Accountability eCRF page. For patients who permanently stop the study medication, the last visit will be replaced by the date of study withdrawal.

12.1. Derivations

Overall Compliance to study medication will be calculated as follows:

$$\frac{Total\ number\ of\ capsules\ taken\ during\ the\ study}{Total\ expected\ number\ of\ capsules\ for\ the\ period} \text{ x } 100\ \%$$

If a patient permanently discontinues study medication, compliance will be determined from Day 1 to the last day of study participation.

13. EFFICACY OUTCOMES

13.1. Primary Efficacy

13.1.1. Primary Efficacy Variable & Derivation

The primary efficacy variable is the proportion of patients with clinical remission at Week 48. Clinical remission is defined as:

- A rectal bleeding sub-score = 0, and
- Endoscopy sub-score = 0 or 1 (excluding friability) and
- A stool frequency sub-score = 0 or 1

The rectal bleeding, endoscopy and stool frequency sub-scores will be obtained from the MMS eCRF page variables MMSRB, MMSMA and MMSST respectively.

13.1.2. Missing Data handling for Primary Efficacy Variable

. Missing data for clinical remission at Week 48 will be imputed as non-responder i.e. not achieved clinical remission. The components used to determine clinical remission will not be imputed.

13.1.3. Primary Analysis of Primary Efficacy Variable

The primary efficacy analysis will be performed for the FAS population.

- Proportion of patients in clinical remission at Week 48 =

$$\frac{Number\ of\ Patients\ with\ Clinical\ Remission\ at\ Week\ 48}{Total\ Number\ of\ Patients\ in\ FAS}$$

Clinical remission at Week 48 will be summarized and graphically presented according to treatment received during the induction study and patient status at the end of the induction study. The proportion of patients in clinical remission at Week 48 with a stool frequency sub score of 0 versus 1 will also be

determined.

13.2. Secondary Efficacy

The secondary efficacy analyses will be performed for the FAS population. Descriptive statistics, excluding SEM, will be presented for all secondary efficacy variables for each measurement timepoint. Change from baseline will also be determined where relevant and is defined in Section **Error! Reference source not found.**.

13.2.1. Secondary Efficacy Variables & Derivations

13.2.1.1. Reduction Relative to Baseline in pMMS at every Visit and MMS at Week 48 and week 96

The MMS ranges from 0 to 9 and is derived from the sum of 3 sub-scores ranging from 0 to 3 for stool frequency, rectal bleeding and mucosal appearance at endoscopy respectively, with a lower score indicating less severe or no UC (See **Error! Reference source not found.**).

Partial MMS is the sum of the stool frequency and rectal bleeding sub-scores of the MMS and will be assessed at every visit.

Descriptive statistics for MMS, pMMS and mean change from baseline (both ISB and BOLS) will be summarized and the number of patients with a reduction in MMS or pMMS relative to ISB and BOLS at each visit will be recorded. Reduction relative to baseline is defined in Section **Error! Reference source not found.**.

Mean MMS at ISB, BOLS, Week 48, and Week 96 will be graphically presented according to treatment received during the induction study and patient efficacy status (remitter, responder/non-responder) at Week 8 of the Induction phase.
Mean pMMS will be graphically plotted by visit.

13.2.1.2. Proportion of Patients with Endoscopic Improvement and/or Endoscopic Remission by Segment at Week 48 and week 96

Endoscopic improvement is defined as an endoscopic sub-score ≤ 1 (excluding friability) and endoscopic remission is defined as an endoscopic sub-score = 0. The improvement and remission will be summarized by segment (descending colon, sigmoid colon, rectum) as well as overall endoscopic improvement and remission for Week 48 and week96.

- Proportion of patients with endoscopic improvement/remission by segment at Week 48/Week 96 =

$$\frac{Number\ of\ patients\ with\ endoscopic\ improvement\ (or\ remission) at\ Week\ 48\ /\ Week\ 96\ in\ segment\ X}{Total\ number\ of\ patients\ in\ FAS}$$

Overall mucosal appearance at endoscopy subscore is equal to the worst segment sub-score. The proportion of patients with overall endoscopic improvement or remission at Week 48/ Week 96 will be calculated as follows:

- Proportion of patients with overall endoscopic improvement/remission at Week 48/Week 96 =

$$\frac{Number\ of\ patients\ with\ overall\ endoscopic\ improvement\ (or\ remission)\ at\ Week\ 48\ /\ Week\ 96}{Total\ number\ of\ patients\ in\ FAS}$$

13.2.1.3. Proportion of Patients with Sustained Endoscopic Improvement and/or Remission at Week 48 and Week 96

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

Proportion of patients with sustained endoscopic improvement at Week 48/Week 96 =

$$\frac{Number\ of\ patients\ with\ endoscopic\ improvement\ at\ Week\ 48/Week\ 96}{Number\ of\ patients\ with\ endoscopic\ improvement\ during\ the\ induction\ study\ (Week\ 8\ )}$$

- Proportion of patients with sustained endoscopic remission at Week 48/Week 96 =

$$\frac{Number\ of\ patients\ with\ endoscopic\ remission\ at\ Week\ 48/\text{Week}\ 96}{Number\ of\ patients\ with\ endoscopic\ remission\ during\ the\ induction\ study\ (Week\ 8\ )}$$

13.2.1.4. Proportion of Patients with Glucocorticoid-free Clinical Remission at Week 48

Glucocorticoid-free clinical remission is defined as clinical remission in addition to not requiring any treatment with glucocorticoids for at least 8 Weeks. Patients using concomitant glucocorticoid medications after Week 40 will be identified using ATC code value H02AB of WHODRUG. Corticosteroids used for treating UC(glucocorticoid) can be identified from CS form of eCRF based on the status.

- Proportion of patients with glucocorticoid-free clinical remission at Week 48 =

$$\frac{Number\ of\ patients\ with\ glucocorticoid\ free\ clinical\ remission\ at\ Week\ 48}{Total\ number\ of\ patients\ in\ FAS}$$

13.2.1.5. Reduction Relative to Baseline in Stool and Rectal Bleeding Frequency at every Study Visit

Frequency and percentage of patients in each stool frequency and rectal bleeding category (see **Error! Reference source not found.**) relative to the number of patients in the FAS will be obtained from the eCRF and summarized for each visit. The number of patients with reduction in stool frequency or improvement in rectal bleeding categories relative to ISB and BOLS will also be presented.

13.2.1.6. Reduction Relative to Baseline (BOLS) in Fecal Calprotectin and CRP Levels at Week 24,Week 48, Week 60, Week 72,Week 84 and Week 96

Change from BOLS in Fecal calprotectin and CRP levels will be determined at Week 24, Week 48, Week 60, Week 72, Week 84, and Week 96. The number of patients with a reduction from BOLS in Fecal calprotectin and CRP levels will also be recorded. Reduction relative to baseline is defined in Section

Error! Reference source not found..

13.2.1.7. Proportion of Patients with Clinical Response at Week 48 and Week 96

Clinical response is defined as a reduction in MMS ≥ 2 points and ≥ 30 % from baseline MMS (BOLS or ISB) with an accompanying decrease in rectal bleeding sub-score ≥ 1 point or absolute rectal bleeding sub-score ≤ 1 point.

- Proportion of patients with clinical response at Week 48 / Week 96 =

$$\frac{Number\ of\ patients\ with\ clinical\ response\ at\ Week\ 48\ /\ Week\ 96}{Total\ number\ of\ patients\ in\ FAS}$$

13.2.1.8. The Inflammatory Bowel Disease Questionnaire Scores and Change from BOLS at Week 24 and Week 48

The IBDQ assesses QoL in patients with inflammatory bowel diseases (IBD). It contains 32 questions covering four health domains (bowel symptoms, systemic symptoms, emotional function and social function) and scores for each question range from 1 (worst case) to 7 (best case). The total IBDQ score is the sum of the individual question scores and ranges from 32 to 224, with higher scores reflecting better well-being. The total scores and change in total score from BOLS IBDQ score will be determined at Week 24 and Week 48 and summarized.

13.2.1.9. Cardiac function as assessed through Echocardiograms

Echocardiography will be performed at the earliest opportunity (Week 24 or Week 48 or Week 72) and will be repeated every six months.
Absolute (%) change-from-previous echocardiogram of Left ventricle Ejection Fraction (LVEF) and in Global Longitudinal Strain (GLS) is calculated.
Clinically relevant reduction (change-from-previous echocardiogram) of LVEF is defined as by > 10% reduction (absolute percentage points) to a value < 50%.

Number of subjects with clinically relevant reduction of LVEF, Number of subjects with a relative percentage reduction in GLS by > 15% from the previous echocardiogram, Number of subjects with a reduction of LVEF > 10% (absolute percentage points) to a value ≥ 50% with an accompanying fall in GLS > 15%. and Number of subjects with reduction in LVEF by > 10% (absolute percentage points) to a value ≥ 50% will be calculated and displayed.

Summary of Actual and Changes from previous echocardiography of other echocardiographic parameters as described in the standard protocol, including 2-dimensional volumes, RV size and systolic function and valve function will also be presented.

All echocardiographic parameters will be presented descriptively and will be reviewed by the Independent Cardiovascular Safety Committee (ICVSC).

13.2.2. Missing Data Handling for Secondary Efficacy Variables

Imputation will not be performed for missing Stool Frequency, Rectal Bleeding and Endoscopy sub score, hence pMMS, and MMS will not be imputed. Missing Fecal calprotectin, CRP scores and IBDQ scores will not be imputed.

Clinical Remission, Clinical Response, Endoscopic Improvement, and Endoscopic remission:

Patients with missing Week 48 assessment will be considered as non-responders i.e. not achieving clinical endpoint at Week 48.

Patients discontinued prior to Week 96 are considered as non-responders at Week 96 i.e. not achieving clinical endpoint at Week 96. LOCF method is used to impute completers (not discontinued but missing Week 96 assessment) by carrying forward the results from Week 48.

13.2.3. Analysis of Secondary Efficacy Variables

Descriptive statistics as described in Section **Error! Reference source not found.** will be presented for the following secondary variables:

- pMMS and MMS scores and change from baseline summary at every visit assessed for overall and by induction study treatment subgroup
- The number and percentage of patients with reduction relative to baseline in pMMS and MMS in

every visit assessed for overall and by induction study treatment subgroup

- The number and proportion of patients with endoscopic improvement and remission, by segment at Week 48 and Week 96
- The number and proportion of patients with sustained endoscopic improvement and remission at Week 48 and Week 96
- The number and proportion of patients with glucocorticoid-free clinical remission at Week 48
- Mucosal appearance at endoscopy by segment at every visit assessed
- Stool frequency and change from baseline at every visit assessed
- Number and percentage of patients with reduction relative to baseline in stool frequency at every study visit
- Rectal Bleeding and change from baseline at every visit assessed
- Number of patients with reduction relative to baseline in rectal bleeding sub-score at each visit
- Frequencies and percentages for rectal bleeding and stool frequency categories (Stool Frequency – 0 or 1 and Rectal Bleeding – 0). Percentages will be plotted graphically by visit.
- Fecal calprotectin and CRP levels and change from baseline summary at every visit assessed for overall and by induction study treatment subgroups
- Number and proportion of patients with reduction relative to baseline in fecal calprotectin and CRP levels at Week 24, Week 48, Week 60, 72, 84, and 96, for overall and by induction study treatment subgroups

- The number and percentage of patients with clinical response at Week 48 and Week 96
- IBDQ scores and change from baseline at Week 24 and Week 48

In addition, the above variables will be included in a listing by patient.

Additionally, loss, new, and sustained responses are also analysed for clinical response and remission.

14. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF. There will be no statistical comparisons between the treatment groups for safety data.

14.1. Adverse Events

Adverse Events (AE) will be coded using the version 25.0 of MedDRA, down to the lower level term (LLT). Only AEs ongoing at the end of the ABX464-103 study and AEs starting on or after the first dose of study medication in the ABX464-104 study will be included in the analysis and description of AEs.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity either on or after the first dose of study medication in the ABX464-104 study.

An overall summary of number of patients within each of the categories described in the sub-sections below, as well as the number of occurrences of the AE will be provided as specified in the templates. Listings will be prepared and will include TEAEs and non-TEAEs.

See **Error! Reference source not found.** for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

14.1.1. All TEAEs

Incidence of TEAEs will be presented by SOC and PT and broken down further by maximum severity and relationship to study medication.

14.1.1.1. SEVERITY

Severity is classed as mild, moderate, severe, life-threatening, and fatal corresponding to the Common Terminology Criteria of Adverse Events (CTCAE) grades 1 to 5 (increasing severity) (Version 5.0 or

most recent version). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

14.1.1.2. RELATIONSHIP TO STUDY MEDICATION

Relationship, as indicated by the Investigator, is classed as Unrelated, Unlikely to be Related, Possibly Related, Probably Related and Related (increasing severity of relationship). TEAEs will be summarized as "Related" or "Unrelated. A "related" TEAE is defined as a TEAE with a relationship to study medication as *"possibly related", "probably related" or "related"* to study medication, and an "unrelated" TEAE is either "*unrelated*" or "*unlikely to be related*" to study medication. TEAEs with a missing relationship to study medication will be regarded as "*probably related"* to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

14.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the response "Permanent discontinuation" to the question "Action taken with study medication" on the AE page of the eCRF. For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

14.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT, as well as related treatment-emergent SAEs by maximum severity will be prepared. Incidence of hospitalization and number of inpatient days will also be summarized. A listing of all SAEs will also be presented.

14.1.4. TEAEs leading to discontinuation from study

TEAEs causing the patient to discontinue from the study will be identified by a positive response to the question “Did the AE cause the patient to discontinue from the study?” and will be summarized by SOC and PT.

14.1.5. Adverse Events Leading to Death

TEAEs leading to death are those events which are recorded as 'Fatal' on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

14.1.6. Adverse Events Of Special Interest

Treatment-emergent adverse events of special interest (AESI) include skin lesions (regardless of its severity), headache episodes, Anaemia, Hepatic enzymes, Serious (grade 3) infections and opportunistic infections, Acute pancreatic adverse events, Malignancies including Non-Melanoma Skin Cancers, More Than 20% Change from Baseline at Week 8 in N-terminal pro b-type Natriuretic Peptide Blood Levels and Cardiac AESIs (See section 8.2 of the protocol for details regarding each of these.). and several Cardiac SOC including Atrial flutter will be recorded as Cardiac AESI. The following TEAEs are recorded as Cardiac AESI:

- Aortic valve disease,
- Asystole,
- Atrial fibrillation,
- Atrial flutter,
- 3rd degree AV block (AV block complete),
- Cardiac arrest,
- Chest pain – cardiac,
- Heart failure,
- Left ventricular systolic dysfunction,
- Mitral valve disease,
- Mobitz (type) II atrioventricular block (type 2, 2nd degree AV block),
- Myocardial infarction,
- Myocarditis, Pericardial effusion,
- Pericardial tamponade,
- Pericarditis,

- Pulmonary valve disease,
- Restrictive cardiomyopathy,
- Right ventricular dysfunction,
- Sick sinus syndrome,
- Tricuspid valve disease,
- Ventricular fibrillation,
- Ventricular tachycardia.

A summary of AESIs by SOC and PT will be prepared, as well as a further summary and listing of information on all AESI and Cardiac AESI.

14.2. Laboratory Evaluations

The central laboratory test results will be included in the reporting of this study. A list of laboratory assessments to be included in the outputs is presented in Table E below. Presentations will use *Systeme International* (SI) Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Shift from baseline according to laboratory approved normal ranges (Low, Normal, High) for quantitative measurements
- Incidence of clinically significant abnormalities as determined by Site Investigator
- Listing of abnormal laboratory results

The following clinical laboratory parameters, except for β-hCG, will be summarized using descriptive statistics as described in section 6.8:

Table E Laboratory Tests

HEMATOLOGY	BIOCHEMISTRY		STOOLS

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

Blood pregnancy results (β-hCG) will be listed by patient for every assessment.

14.3. ECG Evaluations

Results from the central ECG Reading Centre will be included in the reporting of this study. The overall assessment of ECG results will be summarized by frequency and percentage of patients in each assessment category for every visit assessed.

Overall assessment of ECG (Investigator's judgment) will be reported as follows:

- Normal
- Abnormal NCS
- Abnormal CS

The following summaries will be provided for ECG data:

- Incidence of overall assessments (normal, abnormal NCS, abnormal CS) included in shift table as an overall count
- Shift from baseline according to overall assessment of ECG (for quantitative measurements and categorical measurements)
- Listing of all ECG results, including those meeting abnormal and CS or NCS criteria

14.4. Vital Signs

Descriptive statistics as described in Section 6.8 will be summarized for all vital sign parameters.

The following vital signs measurements will be reported for this study:

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (bpm)
- Body Temperature (^{0}C)
- Weight (kg)
- Baseline (ISB) Height (cm)
- BMI (kg/m^2)

The following summaries will be provided for vital signs data:

- Actual and change from baseline (BOLS) by visit
- Incidence of abnormal CS/NCS results for each parameter and visit
- Shift table for number of patients with at least one abnormal result
- Listing of results by patient, including abnormal CS or NCS observations

14.5. Physical Examination

The following assessments will be taken at every physical examination: eyes, ears, nose and throat, lungs/thorax, heart/cardiovascular system, abdomen, skin and mucosae, nervous system, lymph nodes, and Musculo-skeletal system.

Results will be captured by the following categories:

- *Normal*
- *Abnormal, NCS*
- *Abnormal, CS*

Only abnormal findings will be presented in a listing.

15. REFERENCES

1. A phase 2b, open-label, efficacy and safety study of ABX464 as maintenance therapy in patients with moderate to severe Ulcerative Colitis. Abivax. Protocol ABX464-104 Version 5.1., 11Jul 2022

2. Abivax. eCRF ABX464-104 Version 10.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the guidelines in the IQVIA Biostatistics Output Conventions.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Day 1 (Baseline)	Baseline
Week 4	W4
Week 8	W8
Week 12	W12
Week 16	W16
Week 20	W20
Week 24	W24
Week 28	W28

Long Name (default)	Short Name
Week 32	W32
Week 36	W36
Week 40	W40
Week 44	W44
Week 48	W48
Week 60	W60
Week 72	W72
Week 84	W84
Week 96	W96
Week 52 (EOS) or Week 100 (EOS)	W52 EOS or W100 EOS

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

i. Site-Patient ID
ii. Date (where applicable)

APPENDIX 2. MAYO SCORE

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

APPENDIX 3. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/Missing	If start date < ABX464-103 study med start date (from eCRF raw.AE.AEPRIOR = Yes) then not TEAE. If start date >= ABX464-103 study med start date (from eCRF raw.AE.AEPRIOR = No) and: 1) Stop date known to be before ABX464-104 study med start date then not TEAE. 2) If stop date is known or partial and is after ABX464-104 study med start date *and severity of AE has worsened on or before start of ABX464-104 study med*, then TEAE. If severity has not worsened, then not TEAE. 3) If stop date is not known, then worst-case severity is assumed i.e. TEAE If start date >= ABX464-104 study med start date, then TEAE.
Partial, but known components show that it cannot be on or after ABX464-104 study med start date	Known/Partial/Missing	Not TEAE
Partial, could be on or after ABX464-103 study med start date, but before ABX464-104 study med start date	Known	If stop date < ABX464-104 study med start date, then not TEAE. If stop date >= ABX464-104 study med start date *and severity worsened on or after start of ABX464-104 study med*, then TEAE. If severity did not worsen then not TEAE.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < ABX464-104 study med start date, then not TEAE. If stop date >= ABX464-104 study med start date *and severity worsened on or after start of ABX464-104 study med*, then TEAE. If severity did not worsen then not TEAE.
	Missing	Assumed TEAE

START DATE	STOP DATE	ACTION
Partial, could be on or after ABX464-104 study med start date,	Known/Partial/Missing	TEAE
Missing	Known	If stop date < ABX464-104 study med start date, then not TEAE. If stop date >= ABX464-104 study med start date, then TEAE.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < ABX464-104 study med start date, then not TEAE If stop date >= ABX464-104 study med start date, then TEAE.
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < ABX464-104 study med start date, assign as prior If stop date >= ABX464-104 study med start date and start date <= end of treatment, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < ABX464-104 study med start date, assign as prior If stop date >= ABX464-104 study med start date and start date <= end of treatment, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < ABX464-104 study med start date, assign as prior If stop date >= ABX464-104 study med start date and start date <= end of treatment, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < ABX464-104 study med start date, assign as prior If stop date >= ABX464-104 study med start date and start date <= end of treatment, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Missing	Known	If stop date < ABX464-104 study med start date, assign as prior If stop date >= ABX464-104 study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < ABX464-104 study med start date, assign as prior If stop date >= ABX464-104 study med start date, assign as concomitant
	Missing	Assign as concomitant

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
Ganesh L	Document Approval (I certify that I have the education, training and experience to perform this task)	28 Mar 2023 17:08:49 UTC
Josianne Nitcheu	Document Approval (I certify that I have the education, training and experience to perform this task)	28 Mar 2023 17:09:22 UTC
Paul GINESTE	Document Approval (I certify that I have the education, training and experience to perform this task)	28 Mar 2023 17:16:35 UTC