Statistical Analysis Plan

ABX464-301

Phase IIa study of ABX464 in moderate to severe active Rheumatoid Arthritis patients

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CONFIDENTIAL

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The undersigned have reviewed and revised this SAP and find it to be consistent with the study requirements:

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GLOSSARY OF ABBREVIATIONS

%CV	Coefficient of Variation
AE	Adverse Event
ALT	Alanine Transaminase (also SGPT)
AM	Arithmetic Mean
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Transaminase (also SGOT)
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Clinical Research Organisation
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria Adverse Event
CV	Coefficient of Variation
DMP	Data Management Plan
DOB	Date of Birth
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GM	Geometric Mean
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IQR	Interquartile Range
ITT	Intention-to-treat

IV	Intravenous
LambdaZ	Terminal phase rate constant
LOCF	Last Observation Carried Forward
LS Mean	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	Millilitre
N	Number of Patients
n	Number of Events
NCS	Not clinically significant
od	Once daily
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
q12h	Every 12 hours
QC	Quality Control
QoL	Quality of Life
RA	Accumulation ratio
RBC	Red Blood Cell
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
WBC	White Blood Cell
µg	Microgram
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale

1 INTRODUCTION

1.1 General

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under ABIVAX Protocol ABX464-301 and should be read in conjunction with the study protocol and case report form (CRF).

This version of the plan has been developed using the protocol Version 4.0 dated 24OCT2019 (and CRF/ Electronic Data Capture (EDC) specifications dated 06FEB2020. Any further changes to the protocol or CRF will be reviewed for potential impact on the SAP which will be amended if it is deemed necessary.

At the time of writing this version of the SAP, recruitment is ongoing.

Draft 1 was reviewed by the Orion project manager, medical writer and statistical reviewer. The analysis plan will be finalised and approved by the sponsor prior to unblinding of study treatment codes for the planned interim analysis and prior to database lock.

1.2 Changes from Protocol

It is stated in the protocol that *"Analysis of efficacy data will be carried out in the Full Analysis Set in which subjects who prematurely terminate the study will be considered failures."*

Sponsor requested by email having 2 efficacy set.

1.3 Changes from Previous Versions of the SAP

No previous versions of the SAP exist.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the safety of ABX464 given at two different doses (100mg and 50 mg) vs placebo in combination with MTX when administered once daily in patients with moderate to severe active Rheumatoid Arthritis.

2.2 Secondary Objectives

The secondary objectives are the followings:

- To evaluate the effects of the different dose groups of ABX464 at Week 2, Week 4, Week 8 and Week 12 on the American College of Rheumatology (ACR) 20/50/70 response and each of its components versus placebo;
- To evaluate the effects of the different dose groups of ABX464 at Week 2, Week 4, Week 8 and Week 12 on disease activity scores (DAS28 scores, simplified disease activity score [SDAI] and clinical disease activity score [CDAI]) versus placebo;
- To evaluate the effects of the different dose groups of ABX464 at Week 2, Week 4, Week 8 and Week 12 on clinical response (DAS28 EULAR good and moderate responses), Low Disease Activity (LDA) or remission (DAS28-ESR remission, ACR/EULAR remission, SDAI and CDAI remission) versus placebo;
- To evaluate the effects of the different dose groups of ABX464 at Week 2, Week 4, Week 8 and Week 12 on the Patient Reported Outcome (PRO), Healthy Assessment Questionnaire – Disability Index (HAQ-DI);
- To evaluate the expression of miR-124 in total blood (determined by qPCR) at baseline and Week 8;
- To evaluate the effects of different dose groups of ABX464 at Week 8 on miR-124 expression in total blood versus placebo;
- To assess the pharmacokinetics of the ABX464 and its main active metabolite N-Glu-ABX464 after oral administration of different daily doses of ABX464 in patients with Rheumatoid Arthritis.

3 STUDY DESIGN

3.1 OVERVIEW

This Phase IIa study is a randomized, double blind, placebo controlled, parallel group, multiple dose study on ABX464 in combination with methotrexate (MTX), in patients with moderate to severe active Rheumatoid Arthritis who have inadequate response to MTX or/and to an anti- tumor necrosis factor alpha (TNFα) therapy, or intolerance to anti-TNFα therapy.

Several experimental and clinical endpoints will be assessed to obtain information on preliminary efficacy in patients with moderate to severe active Rheumatoid Arthritis. Although no formal hypothesis will be tested, these endpoints will enable a broader understanding of the mechanism of action and potential for clinical efficacy of ABX464 in Rheumatoid Arthritis. No interim analysis is planned.

Up to 60 patients will be randomized in this study. These patients will be enrolled in approximately 20 sites located in Europe. At the beginning, the first 6 patients will be randomized to receive either ABX464 50mg (n=4) or its matching placebo (n=2). The Data Safety Monitoring Board (DSMB) will review the safety of these first 6 patients dosed for at least 2 weeks. Once the DSMB recommendation is granted, the next patients will be randomized to receive either ABX464 50mg, ABX464 100mg or placebo. Then, a second DSMB meeting will be held after the next 6 patients are randomized to check the tolerability

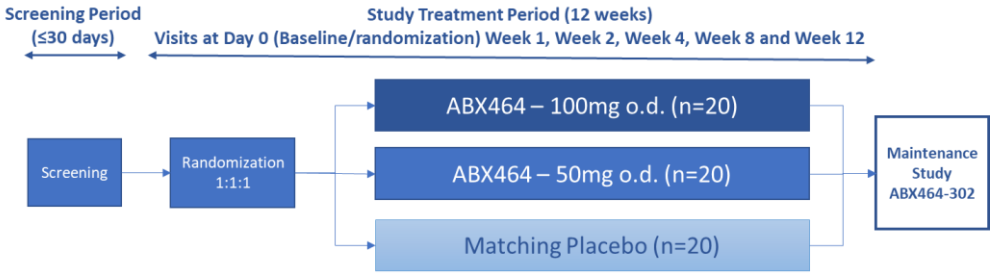
of the 100mg dose. Once the DSMB recommendation is granted, the next patients will be randomized to receive either ABX464 50mg, ABX464 100mg or placebo. The study randomization ratio is 1:1:1.

The recruitment period is between Q2 2019 and Q3 2020, the overall study period is between Q2 2019 and Q1 2021.

Patients will be treated for 12 weeks, followed by a follow-up period (21 days). The total duration of participation in the study will be approximately 15 to 19 weeks from screening to the last study visit (screening and baseline could occur at the same visit). From Baseline / Day 0 onwards, randomized patients will be seen at the investigational site after 1 Week (Day 7), 2 weeks (Day 14), 4 weeks (Day 28), 8 weeks (Day 56) and 12 weeks (Day 84).

At Week 12 (Day 84 +/- 2 days), patients willing to carry on the study treatment will be able to take part in an open-label study (ABX464-302). In any other case, the subjects will exit the study (EOS) and will be treated according to the standard of care. The ABX464-302 follow-up study is a separate clinical study subject to health authorities and ethics committee approvals.

Study scheme:



3.2 INCLUSION AND EXCLUSION CRITERIA

To be eligible for inclusion into this study, each patient must fulfil all inclusion criteria and not violate any exclusion criteria (for the protocol under which they are entered) during screening prior to randomisation.

3.2.1 Inclusion criteria

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

- Men or women age 18 - 75 years;
- Patient with a confirmed and documented diagnosis of adult-onset rheumatoid arthritis, for at least 12 weeks, according to the revised 2010 ACR-EULAR classification criteria, including at least one positive criteria among the following: Rheumatoid Factor (RF), Anti-Citrullinated Peptide Antibody (ACPA) or bone erosion;
- Swollen joint count of ≥ 4 (28-joint count) and tender joint count ≥4 (28-joint count) at screening;
- Patient with a moderate to severe disease activity score DAS28 CRP of ≥ 3.2 and CRP ≥ 5 mg/L (≥ 4.76 nmol)/L) at screening;

- Patient who had an inadequate response (IR), or failed either methotrexate (MTX) or/and anti-TNFα therapy (both administered for at least 12 weeks before IR) or were intolerant to anti-TNFα therapy.
  In addition, MTX treatment should be given at a stable dose ≥ 10 mg/week (for at least 4 weeks prior to randomization). The maximal dose of methotrexate should not exceed a total of 20 mg/week. MTX treatment should be associated with folic acid at a dose ≥ 5 mg/week.
  For the anti-TNFα therapy, the following wash-out period will be required:
  - 30 days prior to randomization for adalimumab and etanercept
  - 2 months prior to randomization for infliximab, certolizumab pegol, golimumab
- Patients with the following hematological and biochemical laboratory parameters obtained within 14 days prior to baseline:
  - Hemoglobin > 9.0 g dL-1;
  - Absolute neutrophil count ≥ 1000 mm-3;
  - Platelets ≥ 100,000 mm-3;
  - Total serum creatinine ≤ 1.3 x ULN (upper limit of normal);
  - Creatinine clearance > 50 mL min-1 by the Cockcroft-Gault equation within 60 days prior to baseline;
  - Total serum bilirubin < 1.5 x ULN;
  - Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 1.5 x ULN;
  - Negative screening for TB and HIV, HCV, HBV
- Patients are able and willing to comply with study visits and procedures as per protocol;
- Patients should understand, sign and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures are performed;
- Patients should be affiliated to a social security regimen (for French sites only);
- Females and males receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 6 months after end of study or early termination. Contraception should be in place at least 2 weeks prior to screening. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (WOCBP) will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception aiming at inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the patient. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle. Female and male patients must not be planning pregnancy and male patients should use condom and must not donate sperm during the trial and for 6 months post completion of their participation in the trial.

3.2.2 Exclusion criteria

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

- Patient with a known positive anti-double stranded deoxyribonucleic acid (DNA [anti-dsDNA]) and confirmed diagnosis of systemic lupus erythematosus (SLE);
- Patients with active infection or the following history of infection(s) (the list is not exhaustive):
    - Active infection (except benign infections, according to investigator's opinion) within 14 days prior to inclusion.
    - Serious infection, defined as an infection requiring hospitalization or IV infusion of anti-infective agents in the 2 months prior to inclusion.
    - A history of opportunistic, recurrent or chronic infections that, in the investigator's opinion, could render this study detrimental to the patient.
- Patients who have received or are expected to receive a live (including attenuated) vaccine within 3 months prior to baseline;
- Acute, chronic or history of clinically relevant (as per investigator's judgement) pulmonary, cardiovascular, hepatic, pancreatic or renal functional abnormality, encephalopathy, neuropathy or unstable CNS pathology such as seizure disorder, angina or cardiac arrhythmias, active malignancy or any other clinically significant medical problems as determined by physical examination and/or laboratory screening tests and/or medical history;
- Acute, chronic or history of immunodeficiency or other autoimmune disease;
- Patient previously treated with any (approved or investigational) non-anti-TNF biological disease-modifying antirheumatic drugs (bDMARDs), and targeted DMARDs (tDMARDS) prior to baseline. These treatments include: IL-6 antagonists, Janus Kinase (JAK) inhibitors, cytotoxic T lymphocyte-associated molecule CTLA-4Fc Chimera, rituximab;
- Patient treated with systemic corticosteroids >10 mg/day during the 2 weeks prior to and at randomization; IV or IM injections of glucocorticoids 4 weeks prior to randomization and IA glucocorticoids 2 weeks prior to randomization;
- Patients treated with other immunosuppressive drugs;
- History of malignancy (other than resected cutaneous basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence) unless it has been treated and a cure is achieved for at least 5 years;
- Serious illness requiring systemic treatment and/or hospitalization within 3 weeks prior to baseline;
- Pregnant or breast-feeding woman;
- Illicit drug or alcohol abuse or dependency;
- Use of any investigational or non-registered product within 3 months or within 5 half-lives preceding baseline, whichever is longer;
- Any condition, which in the opinion of the investigator, could compromise the patient's safety or adherence to the study protocol.

-

3.3 Study Treatment

Medications:

- ABX464 or its matching placebo administered once daily;
- MTX ≥ 10 mg/week, at stable dose, throughout the study; the maximal dose of methotrexate should not exceed a total of 20 mg/week;
- Folic acid ≥ 5 mg/week post MTX dose, to minimize MTX toxicity.

A total of 60 patients will be recruited sequentially to receive the following doses:

	Intervention/treatment Active Arm
Group #1 (n=20): 100mg qd	2 capsules of 50mg ABX464
Group #2 (n=20): 50mg qd	1 capsule of 50mg ABX464 + 1 capsule of matching placebo
Group #3 (n=20): Placebo	2 capsules of matching Placebo

3.4 Study Timepoints

Eligible patients will be enrolled in study at the screening visit within 30 days prior to the first dosing / randomization (screening and baseline could occur at the same visit, if all laboratory results are available).

Patients will be treated for 12 weeks, followed by a follow-up period (21 days).

From Baseline / Day 0 onwards, randomized patients will be seen at the investigational site after 1 Week (Day 7), 2 weeks (Day 14), 4 weeks (Day 28), 8 weeks (Day 56) and 12 weeks (Day 84).

At Week 12 (Day 84 +/- 2 days), patients willing to carry on the study treatment will be able to take part in an open-label study (ABX464-302). In any other case, the subjects will exit the study (EOS) and will be treated according to the standard of care. The ABX464-302 follow-up study is a separate clinical study subject to health authorities and ethics committee approvals.

The end of study (EOS) visit will be performed three weeks after the end of treatment period.

The total duration of participation in the study will be approximately 15 to 19 weeks from screening to the last study visit (screening and baseline could occur at the same visit).

If more than one visit occurs within a window, the nearest to the scheduled time will be presented within the summaries.

See Section 16.1 for the Study Schedule.

Visits and visit windows will be as follows:

Visit		Day	Window
1	Screening	-30 to -1	
2	Baseline	0	
3	Week 1	7	± 2 days
4	Week 2	14	± 2 days
5	Week 4	28	± 2 days
6	Week 8	56	± 2 days
7	Week 12	84	± 2 days
8	Week 15	105 (Follow-up)	± 2 days

3.5 Sample Size Considerations

The primary efficacy endpoint is the rate of subjects meeting the ACR20. This response rate will be compared in subjects who received a given dose of ABX464 or placebo by likelihood ratio chi-square test. The result of the test will be interpreted in a descriptive manner therefore no adjustment for multiple comparison is applied.

For the sample size assessment, the following assumptions will be made:

- Response rate (ABX464): 0.65
- Response rate (placebo): 0.25

According to literature the ACR20 response rate for ABX464 + MTX treated subjects is expected to be between 50% and 65% while that in the placebo + MTX group is assumed to be approximately 25 to 30% (Xeljanz® Summary of Product Characteristics; ORAL Standard Investigators - N Engl J Med 2012; 367:508-519 August 9, 2012).

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

If the above assumptions and definitions hold true with a sample size of 60 subjects receiving two doses of ABX464 or placebo in a ratio of 1:1:1 the study has 84% power to show a difference in response rate between one active study group and placebo.

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

Primary safety endpoint is the rate of all treatment emergent adverse experiences. The above sample size is sufficient to detect an increase in general treatment emergent adverse experience rate from 10% to 50% with 89% power by likelihood ratio chi-square test on a 10%, two-sided significance level.

If approximately 20 subjects receive ABX464 the study has 88% chance to detect at least 1 specific treatment emergent AE if the underlying rate of occurrence is 1:10. When the underlying rate of occurrence is around 1:20 the sample size of 40 subjects receiving active treatment is sufficient to observe at least 1 such an event with a probability of 87% in the active treatment group.

3.6 RANDOMISATION

Eligible patients (i.e. those who fulfil all inclusion/exclusion criteria) will be randomized according to a 1:1:1 ratio into ABX464 100mg, ABX464 50mg or placebo treatment arms.

Up to 60 patients will be randomized in this study. At the beginning, the first 6 patients will be randomized to receive either ABX464 50mg (n=4) or its matching placebo (n=2). The Data Safety Monitoring Board (DSMB) will review the safety of these first 6 patients dosed for at least 2 weeks. Once the DSMB recommendation is granted, the next patients will be randomized to receive either ABX464 50mg, ABX464 100mg or placebo. Then, a second DSMB meeting will be held after the next 6 patients are randomized to check the tolerability of the 100mg dose. Once the DSMB recommendation is granted, the next patients will be randomized to receive either ABX464 50mg, ABX464 100mg or placebo.

Randomization will be performed via a centralized treatment allocation system that will be available 24 hours-a-day, 7 days-a-week. Randomization will be stratified according to previous exposure to anti-TNFα therapy. The bottle numbers to be used for a specific patient will be assigned according to a pre-defined randomization list.

4 STUDY VARIABLES AND COVARIATES

4.1 PRIMARY VARIABLE

The primary variable for statistical comparison between treatment groups will be the incidence of treatment-emergent adverse events in the ABX464 treated Patients versus placebo, categorized by severity.

4.2 SECONDARY EFFICACY VARIABLES

The following secondary efficacy variables will be analysed:

4.2.1 Main Secondary Efficacy Endpoint

Proportion of patients achieving a categorical ACR20 response at Week 12.

The components of ACR20 assessment include:

- C-Reactive Protein (CRP) (mg/L),
- Tender/painful joint count (TJC) (28 joints),
- Swollen joint count (SJC) (28 joints),
- Patient assessment of joint pain (Pain-VAS),
- Patient global assessment of disease (PtGA),

- Physician's Global Assessment of Disease (PrGA),
- HAQ-DI

4.2.2 Other secondary endpoints

- Change from Baseline in the following disease parameters at Week 2, Week 4, Week 8 and Week 12:
    - Individual components of the ACR20 response (CRP, TJC(28), SJC(28), Pain-VAS, PtGA, PrGA, HAQ-DI)
    - Erythrocyte Sedimentation Rate (ESR);
    - DAS28-CRP and DAS28-ESR. The components of DAS28 assessment include TJC(28), SJC(28), CRP/ESR, and PtGA;
    - SDAI score which includes TJC(28), SJC(28), CRP, PtGA, and PrGA;
    - CDAI score which includes TJC(28), SJC(28), PtGA, and PrGA;
    - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score
- Proportion of patients achieving at Week 2, Week 4, Week 8 and Week 12:
    - ACR20/50/70 response
    - Categorical DAS28-CRP response. Proportion of patients achieving categorical DAS28-CRP response will be measured as moderate/good European League Against Rheumatism (EULAR) response at each assessment time point;
    - Low Disease Activity (LDA) (DAS28 ≤ 3.2)
    - DAS28-ESR remission (DAS28 < 2.6)
    - ACR/EULAR remission (TJC(28), SJC(28), CRP, and PtGA: all≤1);
    - SDAI remission (SDAI ≤ 3.3);
    - CDAI remission (CDAI ≤ 2.8).
- Concentration of miR-124 expression in total blood (determined by qPCR) at baseline and week 8
- Change from Baseline in miR-124 expression in total blood at Week 8
- PK parameters:
    - Pre-dose plasma concentration of ABX464/N-Glu at Week 2 and Week 8;
    - Post-dose plasma concentration of ABX464/N-Glu at 1-, 2- and 3-hours post-dose at Baseline, Week 2 and Week 8;
    - Trough plasma concentration of ABX464/N-Glu at End of Study Visit
- The number of incidences of treatment-emergent serious adverse events;
- The number of incidences of treatment-emergent adverse events of special interest;
- The number of incidences of adverse events leading to investigational product discontinuation;
- The number of incidences of clinically significant laboratory abnormalities;
- The number of incidences of all AE (causally related and non-related) and SAE, further categorized by severity.

4.3 Pharmacokinetic Variables

Pharmacokinetics will be measured via serum levels of plasma.

4.4 Pharmacodynamic Variables

No pharmacodynamic variables will be measured.

4.5 Other Outcome Variables

Not applicable.

4.6 Safety Variables

Safety will be evaluated by the following:

- Adverse events
- Laboratory parameters
- Vital signs (body temperature, weight, systolic and diastolic blood pressure, heart rate and respiratory rate)
- Physical examination
- ECG (PR, QRS, QT and QTc and Result: Normal, Abnormal NCS or Abnormal CS)

5 DEFINITIONS AND DERIVED VARIABLES

5.1 Definitions

Study Drug: Study drug is taken to mean either ABX464 or placebo.

Baseline: Baseline is defined by patient and by variable as the last non-missing value before the first dose of study drug

Study Day: Study day is the number of days since start of treatment where the date of first dose is counted as Day 0.

Treatment Exposure: Treatment exposure is the number of days during the treatment period that the patient was exposed to the study treatment and is calculated as:

(Date_of_last_dose) – (Date_of_first_dose) + 1

Compliance: Compliance is the number of doses actually taken divided by the scheduled number of doses expressed as a percentage.

Non-compliance: Non-compliance is defined as taking less than 80% or more than 120% of study medication.

Protocol Deviation: a deviation related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment. This refers to any change, divergence, or departure from the study design or procedures defined in the protocol. Deviations recorded by the Project Manager or CRA, or detected by Data Management or by Statistical programming checks as described in Section 6.3 will be identified and discussed at the Data Review Meeting before database lock to agree which should be included in Listing 16.2.2.

Screening and enrollment: Screening is the process of active evaluation of potential participants for enrollment in a trial. After a patient is recruited, screening occurs during the enrollment period to see if they meet the inclusion and exclusion criteria. If they meet the criteria, the subject is eligible to enroll in the trial.

Baseline and Screening failure: A patient is considered to be a baseline failure if the patient signs the informed consent but withdraws before the screening visit. A patient who does not fulfil the randomization criteria will be considered as a screening failure.

5.2 DERIVED VARIABLES

5.2.1 Disease Activity Score (DAS) 28-CRP (DAS28-CRP) and DAS28-ESR

The components of the DAS28 include:

- tender/painful joint count (TJC) (28),
- swollen joint count (SJC) (28),
- CRP (in mg/L) or ESR (in mm/h), and
- patient global assessment of disease (PtGA), expressed as a Visual Analog Scale (VAS) from 0 to 100 mm

They are calculated with the following formula:

DAS28-CRP = 0.56 $\sqrt{}$ (TJC28) + 0.28 $\sqrt{}$ (SJC28) + 0.36 Ln [CRP(mg/L) + 1] + 0.014 PtGA(VAS100mm) + 0.96

DAS28-ESR = 0.56 $\sqrt{}$ (TJC28) + 0.28 $\sqrt{}$ (SJC28) + 0.70 Ln [ESR(mm/h)] + 0.014 PtGA(VAS100mm)

5.2.2 Simplified Disease Activity Index (SDAI)

This composite index is defined by this equation:

SDAI = TJC28 + SJC28 + PtGA + PrGA + CRP

- PtGA is expressed as a VAS from 0 to 10 cm,
- Investigator global assessment of disease (PrGA) is expressed as a VAS from 0 to 10 cm, and
- CRP (mg/L).

5.2.3 Clinical Disease Activity Index (CDAI)

This composite index is defined by this equation (no acute phase reactant):

CDAI = TJC28 + SJC28 + PtGA + PrGA

- PtGA is expressed as a VAS from 0 to 10 cm,
- PrGA is expressed as a VAS from 0 to 10 cm.

5.2.4 Categorical DAS28-CRP response

Proportion of patients achieving categorical DAS28-CRP response will be measured as moderate/good European League Against Rheumatism (EULAR) response.

The EULAR response criteria are defined as follows:

DAS28 improvement →	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
Present DAS28↓			
≤ 3.2	good response	moderate response	no response
> 3.2 and ≤ 5.1	moderate response	moderate response	no response
> 5.1	moderate response	no response	no response

5.2.5 DAS28-ESR remission

A remission is considered when DAS28-ESR <2.6.

5.2.6 Low Disease Activity (LDA)

The limit to consider a Low Disease Activity (LDA) is: DAS28-ESR ≤ 3.2.

5.2.7 SDAI remission

The SDAI remission is considered achieved if the SDAI score ≤ 3.3.

5.2.8 CDAI remission

The CDAI remission is considered achieved if the CDAI score ≤ 2.8.

5.2.9 ACR/EULAR remission:

In 2011, the American College of Rheumatology (ACR) and EULAR decided to set new criteria to define RA remission.

Boolean-based criteria to be used for clinical trials are:

- Tender/painful Joint Count (28)
- Swollen Joint Count (28)
- CRP
- Patient Global assessment of disease (PtGA) [VAS scale 0 – 10cm]

All ≤ 1.

5.2.10 Categorical ACR20/50/70 response

The component of ACR assessment include:

- tender/painful joint count (28),
- swollen joint count (28),
- patient assessment of joint pain,
- Patient Global Assessment of Disease (PtGA)
- Physician's Global Assessment of Disease (PrGA),

- CRP and
- Disability index of the healthy assessment questionnaire (HAQ-DI).

Patient assessment of joint pain: VAS scale 0-10 cm.

PtGA: Patient Global Assessment of disease activity (VAS scale 0 – 10cm).

PrGA: Physician Global Assessment of disease activity (VAS scale 0 – 10cm).

HAQ-DI: This patient reported outcome questionnaire is usually self-administered by the patient.

The following 8 categories are assessed by the HAQ-DI:

1. Dressing and grooming
2. Arising
3. Eating
4. Walking
5. Hygiene
6. Reach
7. Grip
8. Common daily activities

The patients report the amount of difficulty they have in performing some of these activities. Each question asks on a scale ranging from 0 to 3 if the categories can be performed without any difficulty (scale 0) up to cannot be done at all (scale 3).

The highest score reported by the patient for any component question of the eight categories determines the score for that category. The sum of the computed categories scores is calculated and divided by the number of categories answered. This gives a total score in the 0 to 3 range.

Definition of the ACR20% response:

- ≥ 20% improvement in tender join counts
- ≥ 20% improvement swollen join counts
- ≥ 20% improvement in 3 of the 5 remaining ACR core set measures:
    - PtGA,
    - PrGA,
    - patient assessment of joint pain,
    - HAQ-DI,

- CRP.

For ACR50% and ACR70%, an improvement of respectively 50 and 70% of the same parameters has to be observed.

5.2.11 Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue:

This questionnaire is a measure to assess the patient fatigue in chronic diseases, and is validated in RA. It includes 13 items.

The FACIT score calculation process is defined as follows:

FACIT-Fatigue Subscale Scoring Guidelines (Version 4) – Page 1

Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE SUBSCALE	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____ =**Fatigue Subscale score**

The FACIT scoring guide identifies those items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all FACIT scales and symptom indices, the higher the score the better the QOL.

Handling missing items: If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

Prorated subscale score = Sum of item scores x N of items in subscale ÷ N of items answered

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The total score is then

calculated as the sum of the un-weighted subscale scores. In addition, a total score should only be calculated if ALL of the component subscales have valid scores.

6 ANALYSIS SETS

Membership of the analysis sets will be reviewed and agreed at a Data Review Meeting (DRM) before database lock.

6.1 FULL ANALYSIS SET

The Full Analysis Set (FAS population) is defined as all patients included in the study, who have received at least one dose of the study treatment, and who have at least one baseline data.

The FAS will be used for examining demographics and other baseline characteristics. Number of doses will be presented on the FAS population.

6.2 SAFETY SET

The Safety dataset (SAF population) is defined as those patients included in the study, who have received at least one dose of the study treatment.

The Safety Set will be used for all safety analyses.

6.3 EFFICACY SET

6.3.1 "raw" Efficacy Set (Efficacy Set 1)

A "raw" efficacy set will take into consideration only patients at time point (N = nb of patients for whom efficacy variables are available at W12).

6.3.2 Efficacy Set with imputation (Efficacy Set 2)

Another efficacy set will use data imputation (LOCF) from Week 4.

If there are no efficacy data available, then the dropout would be considered as treatment failure.

6.4 PER PROTOCOL SET

The Per Protocol dataset (PP population) is defined as those patients of the FAS population without any major protocol deviation.

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

- Noncompliance with the inclusion or exclusion criteria;
- Noncompliance with the study treatment;

- Intake of prohibited medication;
- Noncompliance with time window.

Limited programming checks e.g. prohibited medication (based on agreed codes), lab results, may be requested and reviewed on an ongoing basis. Other potential exclusions e.g. incorrect dosing of study medication may be discussed at the DRM. The final decision on inclusion in the PP Set will be agreed and documented before database lock.

7 SAFETY MONITORING

An independent Data Safety Monitoring Board (DSMB), with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee effective protection of patients, ensure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial. Besides, the DSMB may recommend the early termination of the trial at any time if an unacceptable toxicity occurs.

The DSMB will meet after the first 6 patients are dosed (50mg or matching placebo) for at least 2 weeks to check the 50mg dose tolerability. Once the DSMB recommendation is granted, the next 6 patients will be randomized to receive either ABX464 50mg, ABX464 100mg or placebo. A second DSMB meeting will then be held when these 6 next patients are treated for at least 2 weeks, to check the 100mg dose tolerability and grant the recommendation to resume patient's randomization.

In addition, from the first DSMB onwards, meetings will be held every month during the study period. The DSMB will also review all potential causally-related Serious Adverse Events within 7 days of the initial report.

A dose limiting toxicity (DLT) is defined as a grade 3 or higher adverse event as defined by the Common Terminology Criteria for Adverse Events (CTC-AE V5.0) considered by a safety review board as probably or definitely related to study treatment. If more than 2 DLTs occur in the first 12 treated patients for at least 14 days, then the enrolment of additional patients in the treatment group will be stopped, otherwise the enrolment of planned patients will be confirmed. In addition, in case of a life threatening (grade 4) adverse reaction enrolment in the treatment group, all treatment of ongoing patients will be immediately discontinued. In both cases, enrolment will only be resumed upon the decision of the sponsor if the Data Safety Monitoring Board can conclude that the causality of the event was unrelated or unlikely related to study treatment.

The DSMB has only a consultative role. It will inform the Sponsor who will decide whether the DSMB recommendation will be followed. A DSMB charter must be available upon submission of the trial (initial protocol) to the respective competent authorities.

The sponsor will prepare the Data Safety Monitoring Board Charter which will define the primary responsibilities of the DSMB, its relationship with other study components, its members, and the purpose and timing of its meetings. The Charter will describe the process for the evaluation of dose limiting toxicities and provide the decision criteria for study continuation.

Leading up to the meeting, the data will be extracted from the EDC Database by the Database Programmer and provided to Abivax.

8 INTERIM ANALYSES

No interim analysis is planned.

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

9 DATA

9.1 eCRF Data

CRF data will be provided by Orion data management to the statistics department as SAS data sets in Orion standard format which will be used for programming the outputs to be included in the CSR. Populated data sets will be available when programming starts. These may contain dummy data if real data is not yet available.

9.2 External Data

9.2.1 Laboratory Data

Results from Local lab will be entered in CRF for Haematology, Chemistry, Pregnancy (Serum/ urine), Thyroid (for applicable sites only) and ESR (additionally for fibrinogen, troponin I & T, prothrombin time and/or INR, depending upon CSP version they get consented to).

The following table displays the clinical laboratory parameters:

HEMATOLOGY	BIOCHEMISTRY
Hemoglobin	Sodium
Hematocrit	Potassium
WBC	Chloride
Neutrophils	Calcium
Lymphocytes	Phosphate
Monocytes	Glucose
Eosinophils	BUN or urea
Basophils	Creatinine
Platelet count	AST / SGOT
ESR	ALT / SGPT
Prothrombin time and/or INR*	Alkaline phosphatase
Fibrinogen*	GLDH
	LDH
	Lipase
	Total cholesterol
	HDL cholesterol
	LDL cholesterol
	gGT
	Total bilirubin
	Total protein
	Albumin
	CRP
	T3, T4, TSH (for French sites only)
	Troponin I & T*

Tests of TB (Quantiferon TB Gold Plus), HIV (anti-HIV Ab), HCV (anti-HCV Ab), HBV (HBsAg, anti-HBs Ab), anti-HCV Ab, will be performed only at screening. * Except at Week 1 & 2

Reference ranges will be provided by the labs before site initiation and the required parameters will be transcribed onto the Data Management Laboratory Reference Range Form by the CRA. The CRA will provide reference ranges to the DM, who will use them to verify data on CRF. Further information or language translations will be provided by the responsible CRA if required.

A negative or positive result will be counted in the tables under number of positive or number of negative values. For a parameter with only a result in the comment stated that it is inferior to a certain value (< X), all data will be flagged where there is a sign "<" to count how many data are inferior to the detection limit.

No external data transfers are scheduled for this study.

9.2.2 Other non-CRF data

There will be no other non-CRF data.

9.3 RANDOMISATION LIST

The randomisation list will be uploaded to a SAS dataset following database lock.

9.4 Programming and Data Review

Programming of analysis datasets, tables, figures and listings will be ongoing during the data management of the study. Outputs for the DSMB will be reviewed, but not fully QCd. Blind outputs may be reviewed by ABIVAX before DBL.

When the final data is considered clean, key listings (to be agreed) will be run and distributed to the study team for review. A blind data review meeting will be held to discuss the outcome of this review, the imputations for the primary endpoint and the protocol deviations. Once all data issues have been resolved and the analysis populations approved, the database will be locked. The final run of outputs and quality control (QC) will then take place.

A Data Review Meeting (DRM) may be held at the discretion of the Client. During this meeting, data listings (agreed in advance and provided by Simbec-Orion a few days before the meeting) will be used to review any outstanding problematic cases where evaluability of the data is unclear. The populations of patients for the statistical analysis and reporting of the study will be agreed and recorded by the study Statistician.

The study Data Manager, Statistician or Statistical Programmer, Project Manager and a Medic of Simbec-Orion will attend the DRM with representatives of Abivax.

10 STATISTICAL METHODS

10.1 General Principles

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".

Data will be summarised by treatment group. A total column showing all patients will be included for baseline and safety summaries. Where appropriate, data will also be summarised by visit with summaries for each visit attended as scheduled and an additional summary for final (last scheduled visit or early withdrawal). The format of the summaries is defined in the shells at the end of this document.

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum) will be presented. Least squares mean (LS mean), standard error (SE) and 95% confidence interval (CI) will be presented in the statistical analysis outputs as appropriate. For PK summaries, arithmetic mean (AM), geometric mean (GM) and coefficient of variation (%CV) will be used to summarise the data. The minimum and maximum statistics will be presented in summary tables to the same number of significant figures as the original data. The mean/AM, median, LS mean, GM, CI, SD and SE will be presented to one more significant than the original data.

For numeric data which includes non-numeric values (e.g. PK data reported as Below Limit of Qualification (BLQ) or lab results reported as < 10 or >100) the following principles will be applied when summarising the data:

- BLQ will be replaced with a value that is ½ of the lower limit of quantification (LLQ);
- Results reported as < x will be treated in the same way as BLQ with LLQ=x;
- Otherwise AM, GM, SD, CI and %CV will not be calculated;
- Whenever meaningful, minimum, median and maximum will be presented based on the reported data (e.g. minimum = <10, median = 20, maximum = >100).

In summary tables of categorical variables, the number of non-missing observations by category will be presented with percentages. The number of missing observations will also be presented when non-zero. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the column. All percentages will be presented to one decimal place.

Patient line plots will use actual time on the time axis. Mean plots will use a linear time scale for the nominal times of the visits and will be labelled by visit. Results from an early withdrawal visit will be excluded.

If changes in severity for the same TEAE have been reported separately but with the same AE number, they will be collapsed to a single AE with maximum severity for the summary tables, but listed as reported.

Classifications of medical history, concomitant medication and adverse events will be sorted alphabetically within the summary tables.

If any laboratory assessments are repeated at the same visit, the result from the repeat assessment will be used in summaries. Both values will be listed.

CRF data collected/ Data collected on the eCRF will be presented within data listings. The data listings will be sorted by treatment group, country, centre number, patient number and visit/week/day. Treatment group will be as allocated (randomised). If any patients receive the wrong treatment this will be flagged in all listings. Visits outside the visit windows will be identified within the listings. For patients who complete the study, the last visit will be described in the listings as '<Day X>'; for those who withdraw early it will be described as 'End of Study'.

The date format for all output presentations will be 'ddMMMyyyy'.

All statistical analysis will be performed using SAS 9.2 or higher.

All hypothesis testing will be carried out at the 5% (2-sided) significance level unless stated otherwise.

P-values will be rounded to four decimal places. P-values less than 0.0001 will be reported as <0.0001 in tables.

If any of the assumptions underlying the formal statistical methods proposed are violated during the analysis of the final data, alternative statistical methods will be used and any changes documented in the statistical methods section of the clinical study report (CSR), including the rationale for use.

10.2 Stratification and Covariate Adjustment

Randomization will be stratified according to a single factor: patients without previous exposure to anti-TNFα therapy versus patients with previous exposure to anti-TNFα.

10.3 Interactions

The interaction between treatment in two different doses and placebo will be investigated for the primary endpoint (incidence of treatment-emergent adverse events categorized by severity).

10.4 Missing Data

For total scores and subscales with missing items the following rule will be used:

If < 50% of the scale items are missing, the total (or subscale total) will be calculated using the mean score of the non-missing items for that scale or subscale to impute a score for the missing items. In practice the score is derived using the formula:

total of non-missing items x number of items in (sub)scale / number of non-missing items

If > 50% of the items were missing, no scale or subscale score will be calculated; the score will be considered missing.

There will be no other imputation of missing data in this study.

10.5 Pooling of Sites

Sites will be pooled for all analyses. There will be no adjustment for centre effect or treatment by centre interaction.

10.6 Multiple Comparisons

There will be no corrections to nominal p-values for multiple comparisons because the results of the tests will be interpreted in a descriptive manner.

10.7 Subgroup Analyses

Not applicable.

10.8 Statistical Issues

Not applicable.

11 STATISTICAL OUTPUT

General principles for layout of the statistical output are described in Section 10.1, including specification of the table columns, and these are illustrated for each unique table in the table shells in Section 15. For clarity and brevity in this document the phrase "by treatment group" is understood for all summaries and is not included within the text of this section.

11.1 PATIENT DISPOSITION

A summary of the number of screened patients, baseline failures, screening failures and reasons for screening failure will be produced for all enrolled patients (*Table 14.1.1*).The patient disposition table (*Table 14.1.2*) will summarise the following data for all randomised patients:

- The number (%) of patients in the FAS,
- The number (%) of patients in the Safety Set,
- The number (%) of patients in the PP Set.

The number (%) of patients who withdraw from the study and the main reason for withdrawal will be summarised. (*Table 14.1.3*)

A listing of all patients with protocol deviations will be presented. A data listing presenting the eligibility for the analysis sets for each patient will also be presented.

11.2 PATIENT CHARACTERISTICS AT BASELINE

11.2.1 Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment arm (*Table 14.1.4*). This analysis will be conducted on the FAS population.

Age will be calculated using Date of Birth (DOB) and Date of first treatment (Visit 1) and presented as age at last birthday as an integer.

BMI is the patient's body weight in kilograms divided by the square of the patient's height in metres.

11.2.2 Medical History and Current Medical Conditions

All conditions will be coded using the version 23.0 of the Medical Dictionary for regulatory Activities (MedDRA) defined in the Data Management Plan. Past medical/surgical history and current medical conditions will be summarised by system organ class (SOC) and preferred term (PT). The number (%) of patients reporting each condition will be presented using the FAS (*Table 14.1.5.1 and 14.1.5.2*).

11.3 EFFICACY ANALYSES

Analysis of efficacy data will be carried out on Efficacy Set 1 and will be repeated for Efficacy Set 2. Treatment comparisons will be ABX464 in two different doses vs. placebo.

11.3.1 Primary Variable

The primary efficacy endpoint of the study, the ACR20 response rate, will be compared in subjects who received a given dose of ABX464 or placebo by likelihood ratio chi-square test on a 10% two-sided level (*Table 14.2.1.1 and Table 14.2.1.2*).

The result of the test will be interpreted in a descriptive manner therefore no adjustment for multiple comparison is applied.

11.3.2 Secondary Variables

Descriptive statistics will be presented by treatment arm for all secondary efficacy variables for each measurement timepoints separately for the study groups:

- Proportion of patients achieving a categorical ACR20 response at Week 12 (*Table 14.2.2.1 and Table 14.2.2.2*).
- Change from Baseline in the individual components of the ACR20 response at Week 2, Week 4, Week 8 and Week 12 (*Table 14.2.3.1 and Table 14.2.3.2*):
    - C-Reactive Protein (CRP) (mg/L),
    - Tender/painful joint count (TJC) (28 joints),
    - Swollen joint count (SJC) (28 joints),
    - Patient assessment of joint pain (Pain-VAS),
    - Patient global assessment of disease (PtGA),
    - Physician's Global Assessment of Disease (PrGA),
    - HAQ-DI.
- Change from Baseline in the following disease parameters at Week 2, Week 4, Week 8 and Week 12:
    - ESR (*Table 14.2.4.1.1 and Table 14.2.4.1.2*);
    - DAS28-CRP (*Table 14.2.4.2.1 and Table 14.2.4.2.2*) and DAS28-ESR (*Table 14.2.4.3.1 and Table 14.2.4.3.2*);
    - SDAI score (*Table 14.2.4.4.1 and Table 14.2.4.4.2*);
    - CDAI score (*Table 14.2.4.5.1 and Table 14.2.4.5.2*);
    - FACIT-Fatigue score (*Table 14.2.4.6.1 and Table 14.2.4.6.2*).
- Proportion of patients achieving:
    - ACR20/50/70 response;
    - Categorical DAS28-CRP response;
    - LDA;
    - DAS28-ESR remission;
    - ACR/EULAR remission;
    - SDAI remission;
    - CDAI remission

  at Week 2, Week 4, Week 8 and Week 12 (*Table 14.2.5.1 and Table 14.2.5.2*).

These statistics include:

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

In addition to descriptive statistics, mixed model analysis of covariance will be conducted for the following measurements:

- The change from baseline in DAS28-CRP and DAS28-ESR;
- The change from baseline in the individual components of the ACR20 response (CRP, TJC(28), SJC(28), Pain-VAS, PtGA, PrGA, HAQ-DI) and in ESR;
- The change from baseline in SDAI and CDAI scores.

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

All other analyses will be descriptive.

11.4 PK Analyses

PK analysis will not be conducted by Simbec-Orion.

11.5 PD analyses

Not applicable.

11.6 Safety Analyses

11.6.1 Adverse Events

An overall summary table will be presented (any adverse event, any treatment emergent adverse event (TEAE), any serious adverse event (SAE), death, any grade 3 or higher adverse events from baseline to the end of Study) (*Table 14.3.1.1*). This analysis will be conducted on SAF population.

Primary safety endpoint, the rate of all treatment emergent adverse experiences, will be compared in subjects who received a given dose of ABX464 or placebo by likelihood ratio chi-square test on a 10% two-sided significance level (*14.3.1.2.1*).

Two periods will be defined for TEAE:

- Period I: any adverse event which occurs or worsens from first dosing to Day 84;
- Period II: any adverse event which occurs after Day 84.

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

- TEAE (*Table 14.3.1.2.2 and Table Table 14.3.1.2.3*);
- Serious TEAE (*Table 14.3.1.3.1 and Table Table 14.3.1.3.2*);
- TEAE leading to drug discontinuation (*Table 14.3.1.4.1 and Table Table 14.3.1.4.2*);
- TEAE of grade 3 or 4 (*Table 14.3.1.5.1 and Table Table 14.3.1.5.2*);

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

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

All adverse events (AE) will be classified using the version of the MedDRA coding dictionary specified in the DHM.

Events will be classified as treatment-emergent if they started or increased in severity on or after the first date and time of medication dosing at Visit 1 and up to study closure or withdrawal date. If an event start date is partial, then the start day, month, year or stop date will be used to determine if the event is treatment-emergent. If the classification of the AE cannot be determined from the data available, then the event will be considered treatment-emergent.

Treatment-emergent adverse events (TEAEs) will be further classified as follows:

Severe TEAEs*:* Severity classified as 'severe' (Common Toxicity Criteria [CTC] grade 3 or 4) or missing.

Serious TEAEs: Serious classified as 'yes' or missing.

Drug-related TEAEs: Relationship to study drug classified as 'related' or missing.

Serious drug-related TEAEs*:* Both serious and drug-related, as specified above.

TEAEs leading to withdrawal from study: Action taken classified as 'discontinued'.

All AE summary tables will show the number (%) of patients having at least one event and the number of events in each treatment group and overall. Median duration of AEs (from baseline to occurrence) will be presented in the tables. Note: If a patient has multiple AEs with the same preferred term, these will be summarised once within the count for N (%) of patients, but each event will be counted within the number of reports n of each AE. Changes in severity of the same AE (if collected) will be counted only once within the number of reports n of each AE.

The following will be presented in listing format within the data summaries:

- Deaths (*Table 14.3.2.1*);

- Serious Adverse Events (*Table 14.3.2.2*);
- Adverse Events which Led to Withdrawal (*Table 14.3.2.3*).

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed within the data listings.

11.6.2 Laboratory Data

For hematology and biochemistry panels, local laboratory will be used.

Descriptive statistics (n, mean, SD, SEM, median, minimum and maximum) for laboratory parameters will be computed at each scheduled assessment (*Table 14.3.3.1 and Table 14.3.3.2*). If relevant for some parameter, change from baseline will also be tabulated.

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

Laboratory data listings will be presented in two ways:

- Abnormal values (presented within the data summaries) (*Table 14.3.3.3*)
- All laboratory data (presented within the data listings)

The absolute values of each parameter will be summarised at each visit.

In addition, shift tables from baseline will be presented.

If lab results are repeated at the same visit, the repeated result will be used in summaries (instead of the original one) provided the sample was taken within the visit window, otherwise the original result will be used. All results will be listed.

Lab results at unscheduled visits will be included in the listings but will not be summarised.

Serum pregnancy data will be listed only.

11.6.3 Vital Signs

Vital signs will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum) (*Table 14.3.4*). Number of patients with at least one abnormal value will be tabulated (counts and percentages) for each parameter in summary shift tables, by group and dose.

Measurements of vital signs will be done at each visit (Blood pressure, Heart Rate, Body temperature).

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

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

11.6.4 Physical Examination

A routine physical examination (including body weight) will be done at each study visit. Physical examinations will cover eyes, ears, nose, throat, lungs/thorax, heart/cardiovascular system, abdomen, skin and mucosae, nervous system, lymph nodes, musculo-skeletal system, and, if applicable, others. Any new clinically relevant finding compared to baseline must be documented as adverse event.

Shift tables will be presented showing changes from baseline to each visit for normal / abnormal physical examination results (*Table 14.3.5*).

11.6.5 Electrocardiogram

Electrocardiograms will be performed at Screening, Baseline / Day 0, Week 8 / Day 56 and at the EOS visit (in case of premature discontinuation only). At least a 12-lead ECG with recordings of at least 6 action potentials in lead II (paper speed 25mm/s, amplitude 10mm/mV) will be measured at a resting position. Resting ECG should be performed before any examinations.

All abnormal findings must be documented in the CRF. Any clinically relevant findings compared to ECG done at Day 0 / Baseline must be documented as adverse events.

The absolute values of PR, QRS, QT and QTc will be summarised at each visit done (screening, baseline, week 8 and EOS) (*Table 14.3.6*).

The number and percentage of the patients with Normal / Abnormal NCS / Abnormal CS ECG results will be summarised.

11.7 Study Drug Exposure and Compliance

Treatment exposure (ABX464 50mg, 100mg or placebo) and compliance (yes/no) will be summarised for the FAS (*Table 14.3.7*).

11.8 Prior and Concomitant Medication

All medications taken by patients on entry to the study or during the study will be recorded in the CRF. Medications will be classified using the version of the World Health Organisation Drug Dictionary (WHODD) coding dictionary defined in the Data Management Plan. The Anatomical Therapeutic Chemical (ATC) Classification and WHO-DRUG PT will be used to list and summarise the data.

If required by client, conmeds can be summarised at 3 levels: ATC levels 1 and 2 and preferred term.

Prior medications are defined as medication that started and stopped before Day 1. Only medications where the stop date is prior to Day 1 will be considered prior. If the stop date is unknown or incomplete and the medications cannot definitely be considered as stopped prior to Day 1 then the medications will be considered as concomitant medications at randomisation or change in concomitant medication, depending on the start date.

Concomitant medications at randomisation are defined as medications that started before Day 1 and either stopped on Day 1 or continued into the study. Partial start dates where the medication cannot

definitely be considered as starting prior to Day 1 will lead to a categorisation of the medications as having started on or after dosing.

Change in concomitant medication is defined as medication that started on or after Day 1. If the medication start or stop dates are partial then the rules for prior and concomitant medication, detailed above will be observed prior to assigning a category.

The number (%) of patients reporting the use of any prior medications and the number (%) of patients taking each drug by ATC classification and PT will be summarised using the FAS (*Table 14.3.8*). This table will be repeated for concomitant medications at randomisation (*Table 14.3.9.1*) and for change in concomitant medication (*Table 14.3.9.2*)

Mandatory concomitant treatments are the followings:

- MTX ≥ 10 mg/week, at stable dose, throughout the study;
- Folic acid ≥ 10 mg/week post MTX dose, to minimize MTX toxicity.

Allowed Concomitant Medications are the followings:

- Corticosteroids at stable dose of prednisone and prednisone equivalent ≤10 mg/day during the study;
- Non-steroidal anti-inflammatory drugs (NSAIDs) at stable dose during the study;
- Antalgics including class III at stable dose during the study;
- Other non-rheumatologic medications.

Potential other concomitant medications (not indicated for rheumatoid arthritis) should be kept at constant dose during the course of the study and properly reported in the medical file of the patient and the eCRF.

Prohibited concurrent medications are the followings:

- Any non-anti-TNFα biological or targeted DMARDs: IL-6 antagonists, JAK inhibitors, CTLA-4Fc Chimera, rituximab;
- Any immunosuppressive drugs;
- Vaccination with live components during the study and up to 8 Weeks after the last dosing;
- Drugs that could interact with ABX464 should be avoided especially the CYP1A2 substrates. The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (rifampicin, clozapine, theophylline, ropinirole, warfarin and methadone). In case of concomitant treatment with ondansetron, the maximal daily dose must be limited to 8 mg;
- Use of any investigational or non-registered product within 3 months preceding baseline.

12 VALIDATION

All tables, figures and listings will be subject to independent quality control and visual review. Unique tables will be independently programmed. Findings will be documented in a quality control form and actions taken will also be documented.

The completed form will be reviewed and signed by both programmers and by the head of biostatistics.

13 LITERATURE CITATIONS/REFERENCES

Not applicable

14 LIST OF TABLES, FIGURES AND LISTINGS

14.1 LIST OF TABLES

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15 SHELLS FOR TABLES, FIGURES AND LISTINGS

The intended layouts for tables, figures and listings are presented. However, it may be appropriate for the Orion programmer to change the layouts, upon review of the data available, for completeness and clarity.

QCd output will be produced as Rich Text Format (.rtf) files for convenient inclusion in the CSR.

Subject to this, the following will apply:

- Layout will be landscape, fixed width, font size 8.
- Each output will have the heading:

  ABX464-301 (left); date ddMMMyyyy (right)
- Table headings will define the analysis set used for the summary/analysis.
- All outputs will have a footer specifying the SAS program path and filename (left); page x/y (right)
- Tables will have a footer specifying the source listing
- Figures will have a footer specifying the source table or listing
- Additional footnotes will be included where appropriate for clarification.
- Treatment group and patient number and will be included in all listings.

ABX464-301 ddMMMyyyy

Table 14.1.1 Screening Failures (All Enrolled Patients)

	Total Enrolled (N=xx)
Total number of enrolled patients	xx
Screened	xx (xx.x%)
Randomised	xx (xx.x%)
Screening failure	xx (xx.x%)
Baseline failure	Xx (xx.x%)
Primary Reason for screening failure	
Inclusion criterion not met	xx (xx.x%)
Exclusion criterion	xx (xx.x%)
Withdrawal by patient	xx (xx.x%)
Etc	

The denominator for each percentage is the number of enrolled patients.

Source: Listing 16.2.1.1 and 16.2.1.2
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ABX464-301 ddMMMyyyy

Table 14.1.2 Patient Disposition (All Randomised Patients)

	ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Full Analysis Set	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Safety Set	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Efficacy Set 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Efficacy Set 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Per Protocol Set	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

The denominator for each percentage is the number of randomized patients in the column.

Source: Listing 16.2.1.1 and 16.2.1.2
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ABX464-301 ddMMMyyyy

Table 14.1.3 Study Termination and Primary Reason for Withdrawal (All Randomised Patients)

	ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Randomised	xx	xx	xx	xx
Completed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Early withdrawal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Main reason for early withdrawal				
Investigator's decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Major protocol violation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Patient's decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Withdrawal of consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

The denominator for each percentage is the number of randomized patients in the column. Completed defined as performed follow-up visit.

Source: Listing 16.2.1.1 and 16.2.1.2
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ABX464-301 ddMMMyyyy

Table 14.1.4 Demographic and Baseline Characteristics (Full Analysis Set)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Age (years)	N	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x
Sex	N	xx	xx	xx	xx
	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Height (cm)	N	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x
Weight (kg)	N	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x
BMI (kg/m2)	N	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x

The denominator for each percentage is the number of non-missing observations within the column
Age was calculated using DOB and date of first treatment (Visit 1) and presented as age at last birthday.
BMI is the patient’s body weight in kilograms divided by the square of the patient’s height in metres.

Source: Listing 16.2.4
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ABX464-301 ddMMMyyyy

Table 14.1.5.1 Medical History (Full Analysis Set)

	ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Any medical/surgical history	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc				

The denominator for each percentage is the number of patients within the column.
Medical history refers to conditions which stopped prior to or at the screening visit.

Source: Listing 16.4.4
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This layout also applies to:
Table 14.1.5.2 Current Medical Conditions (Full Analysis Set) [Programmer's Note: Update footnote to medical conditions definition.]

ABX464-301 ddMMMyyyy

Table 14.2.1.1 Analysis of ACR20 Response Rate (Efficacy Set 1)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	p-value
ACR20 Response	N	xx	xx	xx	
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Chi-squared test					x.xxxx

Response rate between treatments is compared using likelihood ratio chi-square test at a two-sided 10% significance level.

Source: Listing 16.2.6
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This layout also applies to:
Table 14.2.1.2 Analysis of ACR20 Response Rate (Efficacy Set 2)
Table 14.2.1.3 Analysis of ACR20 Response Rate (PP Set)

ABX464-301 ddMMMyyyy

Table 14.2.2.1 Summary of Categorical ACR20 Response at Week 12 (Efficacy Set 1)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)
Week 12	N	xx	xx	xx
	Rate	xx.x %	xx.x %	xx.x %
	Stratified 95% CI	xx.x % - xx.x %	xx.x % - xx.x %	xx.x % - xx.x %

Source: Listing 16.2.6
Path\Filename

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This layout also applies to:
Table 14.2.2.2 Summary of Categorical ACR20 Response at Week 12 (Efficacy Set 2)

ABX464-301 ddMMMyyyy

Table 14.2.3.1 Analysis of the individual components of the ACR20 response (Efficacy Set 1)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	p-value
CRP					
Baseline	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Stratified 95% CI	xx.xx – xx.xx	xx.xx – xx.xx	xx.xx – xx.xx	
	SD	xx.xx	xx.xx	xx.xx	
	Minimum	xx.x	xx.x	xx.x	
	Maximum	xx.x	xx.x	xx.x	
	Median	xx.xx	xx.xx	xx.xx	
	Quartiles	xx.xx – xx.xx	xx.xx – xx.xx	xx.xx – xx.xx	
Week 2	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Etc				
Change from baseline to Week 2	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Etc				
Analysis of Covariance (change from baseline to Week 2)					x.xxxx
Week 4	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Etc				
Etc					

Etc

Mixed model analysis of covariance is conducted for the changes of baseline for each parameter.

Source: Listing 16.4.5.1
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Programmer's Note: list of variables consists of CRP, TJC, SJC, Pain-VAS, PtGA, PrGA, HAQ-DI.

This layout also applies to:
Table 14.2.3.2 Analysis of the individual components of the ACR20 response (Efficacy Set 2)

ABX464-301 ddMMMyyyy

Table 14.2.4.1.1 Analysis of ESR (Efficacy Set 1)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	p-value
Baseline	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Stratified 95% CI	xx.xx – xx.xx	xx.xx – xx.xx	xx.xx – xx.xx	
	SD	xx.xx	xx.xx	xx.xx	
	Minimum	xx.x	xx.x	xx.x	
	Maximum	xx.x	xx.x	xx.x	
	Median	xx.xx	xx.xx	xx.xx	
	Quartiles	xx.xx – xx.xx	xx.xx – xx.xx	xx.xx – xx.xx	
Week 2	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Etc				
Change from baseline to Week 2	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Etc				
Analysis of Covariance (change from baseline to Week 2)					x.xxxx
Week 4	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	
	Mean	xx.xx	xx.xx	xx.xx	
	Etc				
Etc					

Mixed model analysis of covariance is conducted for the changes of baseline for each parameter.

Source: Listing 16.4.5.2
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This layout also applies to:
Table 14.2.4.1.2 Analysis of ESR (Efficacy Set 2)
Table 14.2.4.2.1 Analysis of DAS28-CRP (Efficacy Set 1)
Table 14.2.4.2.2 Analysis of DAS28-CRP (Efficacy Set 2)
Table 14.2.4.3.1 Analysis of DAS28-ESR (Efficacy Set 1)
Table 14.2.4.3.2 Analysis of DAS28-ESR (Efficacy Set 2)
Table 14.2.4.4.1 Analysis of SDAI Score (Efficacy Set 1)
Table 14.2.4.4.2 Analysis of SDAI Score (Efficacy Set 2)
Table 14.2.4.5.1 Analysis of CDAI Score (Efficacy Set 1)
Table 14.2.4.5.2 Analysis of CDAI Score (Efficacy Set 2)

ABX464-301 ddMMMyyyy

Table 14.2.4.6.1 Summary of FACIT-Fatigue Score (Efficacy Set 1)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)
Baseline	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Mean	xx.xx	xx.xx	xx.xx
	Stratified 95% CI	xx.xx – xx.xx	xx.xx – xx.xx	xx.xx – xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x
	Median	xx.xx	xx.xx	xx.xx
	Quartiles	xx.xx – xx.xx	xx.xx – xx.xx	xx.xx – xx.xx
Week 2	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Mean	xx.xx	xx.xx	xx.xx
	Etc			
Change from baseline to Week 2	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Mean	xx.xx	xx.xx	xx.xx
	Etc			
Week 4	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Mean	xx.xx	xx.xx	xx.xx
	Etc			
Etc				

Source: Listing 16.4.5.2
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This layout also applies to:
Table 14.2.4.6.2 Summary of FACIT-Fatigue Score (Efficacy Set 2)

ABX464-301 ddMMMyyyy

Table 14.2.5.1 Summary of Patients Achieving Different Responses and Remissions (Efficacy Set 1)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)
ARC20 Response				
Week 2	N	xx	xx	xx
	Rate	xx.x %	xx.x %	xx.x %
	Stratified 95% CI	xx.x % - xx.x %	xx.x % - xx.x %	xx.x % - xx.x %
Week 4	N	xx	xx	xx
	Rate	xx.x %	xx.x %	xx.x %
	Stratified 95% CI	xx.x % - xx.x %	xx.x % - xx.x %	xx.x % - xx.x %
Etc				
Etc				

Source: Listing 16.4.5.3
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Programmer's Note: list of variables consists of ACR20/50/70 response, Categorical DAS28-CRP response, LDA, DAS28-ESR remission, ACR/EULAR remission, SDAI remission, CDAI remission.

This layout also applies to:
Table 14.2.5.2 Summary of Patients Achieving Different Responses and Remissions (Efficacy Set 2)

ABX464-301 ddMMMyyyy

Table 14.3.1.1 Summary of Adverse Events (Safety Set)

	ABX-464 100mg (N=xx)		ABX-464 50mg (N=xx)		Placebo (N=xx)		Total (N=xx)	
	n	N (%)	n	N (%)	n	N (%)	n	N (%)
Any Adverse Event	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Any Treatment-Emergent Adverse Event	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Any Serious Adverse Event	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Adverse Event leading to death	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Any grade 3 or higher Adverse Event	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)

The table presents number of events (n) and number and percentage of patients (N(%)).
The denominator for each percentage is the number of patients within the column.

Source: Listing 16.2.7
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ABX464-301 ddMMMyyyy

Table 14.3.1.2.1 Analysis of Treatment-Emergent Adverse Events (Safety Set)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	p-value
Any Treatment-Emergent Adverse Event	N	xx	xx	xx	
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Chi-squared test					x.xxxx

The denominator for each percentage is the number of patients within the column
TEAE rate between treatments is compared using likelihood ratio chi-square test at a two-sided 10% significance level.

Source: Listing 16.2.7
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ABX464-301 ddMMMyyyy

Table 14.3.1.2.2 Treatment-Emergent Adverse Events, by SOC and PT: Period 1 (Safety Set)

	ABX-464 100mg (N=xx)			ABX-464 100mg (N=xx)			Placebo (N=xx)			Total (N=xx)		
	n	N (%)	duration (days)	n	N (%)	duration (days)	n	N (%)	duration (days)	n	N (%)	duration (days)
Any Treatment-Emergent Adverse Event	xx	xx (xx.x%)		xx	xx (xx.x%)		xx	xx (xx.x%)		xx	xx (xx.x%)	
SOC	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx
PT	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx
PT	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx
SOC	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx	xx	xx (xx.x%)	xx.xx
Etc												
Etc												

The table presents number of events (n) and number and percentage of patients (N(%)).
The denominator for each percentage is the number of patients within the column.
Duration (days) represents median duration of AEs (from baseline to occurrence).

Source: Listing 16.2.7
Path\Filename

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This layout also applies to:
Table 14.3.1.2.3 Treatment-Emergent Adverse Events, by SOC and PT: Period 2 (Safety Set)
Table 14.3.1.3.1 Serious Treatment-Emergent Adverse Events, by SOC and PT: Period 1 (Safety Set)
Table 14.3.1.3.2 Serious Treatment-Emergent Adverse Events, by SOC and PT: Period 2 (Safety Set)
Table 14.3.1.4.1 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation, by SOC and PT: Period 1 (Safety Set)
Table 14.3.1.4.2 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation, by SOC and PT: Period 2 (Safety Set)
Table 14.3.1.5.1 Treatment-Emergent Adverse Events of Grade 3 or 4 by SOC and PT: Period 1 (Safety Set)
Table 14.3.1.5.2 Treatment-Emergent Adverse Events of Grade 3 or 4 by SOC and PT: Period 2 (Safety Set)

ABX464-301 ddMMMyyyy

Table 14.3.2.1 Listing of Deaths (Safety Set)

Treatment	Patient number	Date of death	Cause of death
xxxxxx	xxx-xxxx	ddMMMyyyy	xxxxxxxxxxxxxxxxxx
xxxxxx	xxx-xxxx	ddMMMyyyy	xxxxxxxxxxxxxxxxxx
Etc			

Path\Filename

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ABX464-301 ddMMMyyyy

Table 14.3.2.2 Listing of Serious Adverse Events

Treatment	Centre/ Patient number	Adverse Event PT SOC	Onset date	Resolution date / ongoing	Outcome	Relationship to study drug	Action taken with study drug	Other action taken
xxxxx	xxx-xxxx	xxxxxxxxxx xxxxxxxx xxxx	ddMMMyyyy	ddMMMyyyy / ongoing	Resolved/ Resolved without sequelae/ Etc	Yes/No	None/ Temporary discontinuation/ Etc	Concomitant medication (CM no.)/ Procedure (PR no.)
		xxxxxxxxxx xxxxxxxx xxxx	ddMMMyyyy	ddMMMyyyy / ongoing	Resolved/ Resolved without sequelae/ Etc	Yes/No	None/ Temporary discontinuation/ Etc	Concomitant medication (CM no.)/ Procedure (PR no.)
		Etc						
Etc								

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This layout also applies to:
Table 14.3.2.3 Listing of Withdrawals Due to Adverse Events (Safety Set)

ABX464-301 ddMMMyyyy

Table 14.3.3.1 Summary of Laboratory Parameters: Haematology (Safety Set)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Haematocrit					
Baseline	N	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	SEM	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x
Week 1	N	xx	Xx	Xx	Xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	Etc				
Change from baseline to Week 1	N	xx	Xx	Xx	Xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	Etc				
Etc					
Etc					

Source: Listing 16.2.8.1

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Programming note: start each parameter on a new page

This layout also applies to:
Table 14.3.3.2 Summary of Laboratory Parameters: Biochemistry (Safety Set)

ABX464-301 ddMMMyyyy

Table 14.3.3.3 Listing of Abnormal Laboratory Values (Safety Set)

Treatment	Patient number	Visit	Laboratory Parameter	Value
xxxxxx	xxx-xxxx	Week x	xxxxxxxxxxxxxxxxxx	xx.xx
			xxxxxxxxxxxxxxxxxx	xx.xx
			Etc	
		Etc		
	Etc			
Etc				

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ABX464-301 ddMMMyyyy

Table 14.3.4 Vital Signs (Safety Set)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Systolic BP (mmHg)					
Baseline	N	xx	xx	xx	xx
	Normal	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Abnormal NCS	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Abnormal CS	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	SEM	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x
Week 1	N	xx	xx	xx	xx
	Normal	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Etc				
Etc					
Etc					

The denominator for each percentage is the number of non-missing observations within the column.
NCS = Not Clinically Significant; CS = Clinically Significant

Source: Listing 16.4.9
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Programmer's Note: list of variables consists of body temperature, weight, systolic and diastolic blood pressure, heart rate and respiratory rate.

ABX464-301 ddMMMyyyy

Table 14.3.5 Shift Table of Physical Examination (Safety Set)

		ABX-464 100mg (N=xx)		ABX-464 50mg (N=xx)		Placebo (N=xx)		Total (N=xx)	
		normal	abnormal	normal	abnormal	normal	abnormal	normal	abnormal
Eyes									
Baseline	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Week 1	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Etc									
Ears									
Baseline	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Week 1	N	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Etc									
Etc									

The denominator for each percentage is the number of non-missing observations within the column.

Source: Listing 16.4.10
Path\Filename

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Programmer's Note: list of variables consists of eyes, ears, nose, throat, lungs/thorax, heart/cardiovascular system, abdomen, skin and mucosae, nervous system, lymph nodes, musculo-skeletal system, and, if applicable, others.

ABX464-301 ddMMMyyyy

Table 14.3.6 Electrocardiogram (Safety Set)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
PR interval					
Baseline	N	xx	xx	xx	xx
	Normal	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Abnormal NCS	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Abnormal CS	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x
Week 1	N	xx	xx	xx	xx
	Normal	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Etc				
Etc					
Etc					

The denominator for each percentage is the number of non-missing observations within the column.
NCS = Not Clinically Significant; CS = Clinically Significant

Source: Listing 16.4.11
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Programmer's Note: The absolute values of PR, QRS, QT and QTc will be summarised at each visit.

ABX464-301 ddMMMyyyy

Table 14.3.7 Study Drug Exposure and Compliance (Full Analysis Set)

		ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Number of dose intakes	N	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x
Study drug exposure (days)	N	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	Etc				
Compliance	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Study drug exposure (days) is calculated as (date of last dose) - (date of first dose) + 1.

Source: Listing 16.2.5
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ABX464-301 ddMMMyyyy

Table 14.3.8 Prior Medications (Full Analysis Set)

	ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Any prior medication[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X, xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0N, xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0NXX, xxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0NXX, xxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0N, xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0NXX, xxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc				
Etc				

[1] Medication that stopped prior to date of first dose.
WHO-DDE version <XX.X>
The denominator for each percentage is the number of patients in the full analysis set within the column.

Source: Listing 16.4.12.1

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This layout also applies to:
Table 14.3.9.1 Concomitant Medications (Full Analysis Set)

ABX464-301 ddMMMyyyy

Table 14.3.9.2 Change in Concomitant Medications (Full Analysis Set)

	ABX-464 100mg (N=xx)	ABX-464 50mg (N=xx)	Placebo (N=xx)	Total (N=xx)
Any concomitant medication	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X, xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0N, xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0NXX, xxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0NXX, xxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0N, xxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
X0NXX, xxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc				
Etc				

WHO-DDE version <XX.X>
The denominator for each percentage is the number of patients in the full analysis set within the column.

Source: Listing 16.4.12.3
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ABX464-301 ddMMMyyyy

Listing 16.2.1.1 Patient Disposition

Treatment	Centre/ Patient number	First dose date	Last dose date	Completed study	Date of completion/ withdrawal	If not completed specify	Did subject complete the follow-up visit?	Death Date
xxxxxx	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	ddMMMyyyy	specify	Yes/No (specify reason)	ddMMMyyyy
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	ddMMMyyyy	specify	Yes/No (specify reason)	ddMMMyyyy
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	ddMMMyyyy	specify	Yes/No (specify reason)	
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	ddMMMyyyy	specify	Yes/No (specify reason)	
Etc								

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ABX464-301 ddMMMyyyy

Listing 16.2.1.2 Discontinued Patients

Treatment	Centre/ Patient number	First dose date	Last dose date	Date of withdrawal	Main reason for withdrawal
xxxxxx	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxxxxxxxxxxxxxxxxxxxxxxxxx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxxxxxxxxxxxxxxxxxxxxxxxxx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxxxxxxxxxxxxxxxxxxxxxxxxx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxxxxxxxxxxxxxxxxxxxxxxxxx
Etc					

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ABX464-301 ddMMMyyyy

Listing 16.2.2 Protocol Deviations

Treatment	Centre/ Patient number	Major deviation	Protocol deviation
xxxxxx	xxx-xxxx	Yes/No	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxx-xxxx	Yes/No	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxx-xxxx	Yes/No	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxx-xxxx	Yes/No	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Etc			

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ABX464-301 ddMMMyyyy

Listing 16.2.3 Analysis Datasets

Treatment	Centre/ Patient number	Full Analysis Set	Per Protocol Set	Safety Set	Efficacy Set 1	Efficacy Set 2
xxxxxx	xxx-xxxx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
	xxx-xxxx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
	xxx-xxxx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
	xxx-xxxx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Etc						

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Listing 16.2.4 Demographic Data

Treatment	Centre/ Patient number	Date of screening	Date of birth	Age (years)	Gender	Race	Weight (kg)	Height (cm)	BMI (kg/m^2)
xxxxxx	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	xx	xxxx	xxxx	xx.x	xxx.x	xx.x
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	xx	xxxx	xxxx	xx.x	xxx.x	xx.x
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	xx	xxxx	xxxx	xx.x	xxx.x	xx.x
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	xx	xxxx	xxxx	xx.x	xxx.x	xx.x
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	xx	xxxx	xxxx	xx.x	xxx.x	xx.x
Etc									

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ABX464-301 ddMMMyyyy

Listing 16.2.5 Study Drug Exposure and Compliance

Treatment	Centre/ Patient number	Date of compliance check	Date of first dose	Date of last dose	Duration of exposure (days)	Capsules used	Capsules expected to be used	Capsules returned	Capsules lost
xxxxxx	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xx	xx	xx	xx	xx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xx	xx	xx	xx	xx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xx	xx	xx	xx	xx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xx	xx	xx	xx	xx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xx	xx	xx	xx	xx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xx	xx	xx	xx	xx
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xx	xx	xx	xx	xx
	Etc								
Etc									

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Listing 16.2.6 Efficacy Response Data: ACR20/50/70 Response

Treatment	Centre/ Patient number	ACR20 Response	ACR50 Response	ACR70 Response
xxxxxx	xxx-xxxx	Yes/No	Yes/No	Yes/No
	xxx-xxxx	Yes/No	Yes/No	Yes/No
	xxx-xxxx	Yes/No	Yes/No	Yes/No
	xxx-xxxx	Yes/No	Yes/No	Yes/No
Etc				

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Listing 16.2.7 Adverse Event Listing

Treatment	Centre/ Patient number	Baseline date	Adverse Event SOC PT	Onset date	Resolution date /ongoing	Outcome	Serious	Severity	Relationship to study drug	Action taken with study drug	Other action taken
xxxxxxx	xxx-xxxx	ddMMMyyyy	xxxxxxxxx xxxxxxxx xxxxxxx	ddMMMyyyy	ddMMMyyyy/ Ongoing	Resolved/resolved without sequelae /Etc	Yes /No	Grade 1/ Grade 2/ etc	Yes/No	None /Temporary discontinuation /Etc	Concomitant medication (CM no.)/ Procedure (PR No.)
		ddMMMyyyy	xxxxxxxxx xxxxxxxx xxxxxxx	ddMMMyyyy	ddMMMyyyy/ Ongoing	Resolved/resolved without sequelae /Etc	Yes /No	Grade 1/ Grade 2/ etc	Yes/No	None /Temporary discontinuation /Etc	Concomitant medication (CM no.)/ Procedure (PR No.)
			Etc								
Etc											

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Listing 16.2.8.1 Laboratory Measurements: Haematology

Parameter	Treatment	Centre/ Patient number	Visit	Was sample taken?	Result	Unit	Investigator's interpretation
Haemoglobin	xxxxxxx	xxx-xxxx	Screening	Yes/ No (reason)	xxx.xx	xxxx	Normal/ Abnormal CS/ Abnormal NCS
			Baseline	Yes/ No (reason)	xxx.xx	xxxx	Normal/ Abnormal CS/ Abnormal NCS
			Week 1*	Yes/ No (reason)	xxx.xx	xxxx	Normal/ Abnormal CS/ Abnormal NCS
			Etc		xxx.xx	xxxx	Normal/ Abnormal CS/ Abnormal NCS
		xxx-xxxx	Screening		xxx.xx	xxxx	Normal/ Abnormal CS/ Abnormal NCS
			Etc				
		Etc					
	Etc						
Etc							

*Outside the visit window
CS=Clinically Significant; NCS=Non Clinically Significant

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This layout also applies to:

Listing 16.2.8.2 Laboratory Measurements: Biochemistry

ABX464-301 ddMMMyyyy

Listing 16.4.1 Final Status

Treatment	Centre/ Patient number	First dose date	Last dose date	Completed treatment	Primary reason for discontinuation (specify)	Was the randomisation code broken? (date and reason)	Will subject enter follow-up?
xxxxxx	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	xxxxxxxxxx (specify)	Yes (ddMMMyyy; xxxxxx)/ No	Yes/No
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	xxxxxxxxxx (specify)	Yes (ddMMMyyy; xxxxxx)/ No	Yes/No
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	xxxxxxxxxx (specify)	Yes (ddMMMyyy; xxxxxx)/ No	Yes/No
	xxx-xxxx	ddMMMyyyy	ddMMMyyyy	Yes/No	xxxxxxxxxx (specify)	Yes (ddMMMyyy; xxxxxx)/ No	Yes/No
Etc							

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Listing 16.4.2 Patient Visit Dates

Treatment	Centre/ Patient number	Visit	Date
xxxxxx	xxx-xxxx	xx	ddMMMyyyy
		xx	ddMMMyyyy
		xx*	ddMMMyyyy
		xx	ddMMMyyyy
Etc			

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Listing 16.4.3.1 Inclusion Criteria

Protocol version: XXXX

Definition of criterion	
1	xxxxxxxxxxxxxxxx
2	xxxxxxxxxxxxxxxx
3	Etc
4	
5	
6	
7	
8	
Etc	

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Programmer's Note: The list of criteria will be presented on the first page of the listing. Patient data will start on page 2. Repeat for each protocol amendment if the criteria change.

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Listing 16.4.3.1 Inclusion Criteria

Treatment	Centre/ Patient number	Protocol version	Criteria								
			1	2	3	4	5	6	7	8	Etc
xxxxxx	xxx-xxxx	x.xx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
	xxx-xxxx	x.xx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
	xxx-xxxx	x.xx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
	xxx-xxxx	x.xx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Etc											

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This layout also applies to:

Listing 16.4.3.2 Exclusion Criteria

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Listing 16.4.4 Medical History

Treatment	Centre/ Patient number	Date of UC Diagnosis	Any other conditions?	Condition SOC PT	Date of diagnosis	Ongoing/ End date
xxxxxx	xxx-xxxx	ddMMMyyyy	Yes/No	xxxxxxxxxxxxx xxxxxxxxxxx xxxxxxxxxx	ddMMMyyyy	Yes/ No (ddMMMyyyy)
		ddMMMyyyy	Yes/No	xxxxxxxxxxxxx xxxxxxxxxxx xxxxxxxxxx	ddMMMyyyy	Yes/ No (ddMMMyyyy)
Etc						

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Listing 16.4.5.1 Raw Efficacy Data: Individual Components of the ACR20 Response

Treatment	Centre/ Patient number	Visit	C-Reactive Protein (CRP) (mg/L)	Tender/ painful joint count (TJC) (28 joints)	Swollen joint count (SJC) (28 joints)	Patient assessment of joint pain (Pain-VAS)	Patient global assessment of disease (PtGA)	Physician's Global Assessment of Disease (PrGA)	HAQ-DI
xxxxxx	xxx-xxxx	Baseline	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		Etc*							
Etc									

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Listing 16.4.5.2 Raw Efficacy Data: ESR, DAS28-CRP, DAS28-ESR, SDAI Score, CDAI Score and FACIT-Fatigue Score

Treatment	Centre/ Patient number	Visit	ESR	DAS28-CRP	DAS28-ESR	SDAI Score	CDAI Score	FACIT-Fatigue Score
xxxxxx	xxx-xxxx	Baseline	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		Etc*						
Etc								

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ABX464-301 ddMMMyyyy

Listing 16.4.5.3 Raw Efficacy Data: Different Responses and Remissions

Treatment	Centre/ Patient number	Visit	Categorical DAS28-CRP response	LDA	DAS28-ESR remission	ACR/EULAR remission	SDAI remission	CDAI remission
xxxxxx	xxx-xxxx	Baseline	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
		Etc*						
Etc								

*Outside the visit window

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Listing 16.4.9 Vital Signs

Treatment	Centre/ Patient number	Visit	Date of visit	Body temperature (°C)	Weight (kg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart rate (beats/min)	Respiratory rate (/min)
xxxxxx	xxx-xxxx	xx	ddMMMyyyy	xx.x	xx.x	xxx	xxx	xxx	xx.x
		xx	ddMMMyyyy	xx.x	xx.x	xxx	xxx	xxx	xx.x
		xx*	ddMMMyyyy	xx.x	xx.x	xxx	xxx	xxx	xx.x
		xx	ddMMMyyyy	xx.x	xx.x	xxx	xxx	xxx	xx.x
Etc									

*Outside the visit window

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ABX464-301 ddMMMyyyy

Listing 16.4.10 Physical Examination

Treatment	Centre/ Patient number	Visit	Date of Visit	Body system	Status	Abnormality
xxxxxx	xxx-xxxx	Screening	ddMMMyyyy	Eyes	Normal/ Abnormal NCS/ Abnormal CS/ Not done	xxxxxxxxxxxxxxxxxxxxxxxxxx
				Ear/Nose/Throat	Normal/ Abnormal NCS/ Abnormal CS/ Not done	xxxxxxxxxxxxxxxxxxxxxxxxxx
				Lungs/Thorax	Normal/ Abnormal NCS/ Abnormal CS/ Not done	xxxxxxxxxxxxxxxxxxxxxxxxxx
				Etc		
		xx*	ddMMMyyyy	Eyes	Normal/ Abnormal NCS/ Abnormal CS/ Not done	xxxxxxxxxxxxxxxxxxxxxxxxxx
				Etc		
Etc						

*Outside the visit window

CS=Clinically Significant; NCS=Non Clinically Significant

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Listing 16.4.11 12-Lead Electrocardiogram

Treatment	Centre/ Patient number	Visit	Date of visit	Time	PR interval (msec)	QRS width (msec)	QT interval (msec)	QTc interval (msec)	Investigator's interpretation	Abnormality
xxxxxx	xxx-xxxx	Baseline	ddMMMyyyy	hh:mm	xx	xx	xx	xx	Normal/ Abnormal NCS/ Abnormal CS	xxxxxxxxxx
		Week 8	ddMMMyyyy	hh:mm	xx	xx	xx	xx	Normal/ Abnormal NCS/ Abnormal CS	xxxxxxxxxx
		Etc*								
	Etc									
Etc										

*Outside the visit window

CS=Clinically Significant; NCS=Non Clinically Significant

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Listing 16.4.12.1 Prior Medications

Treatment	Centre/ Patient number	Therapy ATC Code PT	Indication	Dose	Unit	Frequency	Route	Start date (Stop date / Ongoing)	Given for pre-existing condition (Related medical history number)	Given for adverse event? (Related adverse event number)
xxxxxx	xxx-xxxx	xxxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxxxx	xxxxxxx	xx.x	xxx	xxx	xxx	ddMMMyyyy (ddMMMyyyy)	Yes (xxx) / No	Yes (xxx) / No
		xxxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxxxx	xxxxxxx	xx.x	xxx	xxx	xxx	ddMMMyyyy (ddMMMyyyy)	Yes (xxx) / No	Yes (xxx) / No
		xxxxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxxxx	xxxxxxx	xx.x	xxx	xxx	xxx	ddMMMyyyy (ddMMMyyyy)	Yes (xxx) / No	Yes (xxx) / No
Etc										

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This layout also applies to:

Listing 16.4.12.2 Concomitant Medications (Programming note: can have stop date as 'ongoing')

Listing 16.4.12.3 Changes to Medications

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Listing 16.4.13 Pregnancy Test

Treatment	Centre/ Patient number	Visit	Test done	Reason not done	Date of test	Result
xxxxxx	xxx-xxxx	Screening	Yes/No/Not applicable	xxxxxxxxxxxxx	ddMMMyyyy	Positive/Negative
		xx	Yes/No/Not applicable	xxxxxxxxxxxxx	ddMMMyyyy	Positive/Negative
		xx*	Yes/No/Not applicable	xxxxxxxxxxxxx	ddMMMyyyy	Positive/Negative
		xx	Yes/No/Not applicable	xxxxxxxxxxxxx	ddMMMyyyy	Positive/Negative
		Etc				
Etc						

*Outside the visit window

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Listing 16.4.14 Laboratory Samples Collection

Parameter	Treatment	Centre/ Patient number	Visit	Sample taken	Reason not done	Date of test	Result	Interpretation
xxxxxx	xxxxxx	xxx-xxxx	Screening	Yes/No	xxxxxxxxxxxxx	ddMMMyyyy	xx	Normal/ Abnormal CS/ Abnormal NCS
			xx	Yes/No	xxxxxxxxxxxxx	ddMMMyyyy	xx	Normal/ Abnormal CS/ Abnormal NCS
			xx*	Yes/No	xxxxxxxxxxxxx	ddMMMyyyy	xx	Normal/ Abnormal CS/ Abnormal NCS
			xx	Yes/No	xxxxxxxxxxxxx	ddMMMyyyy	xx	Normal/ Abnormal CS/ Abnormal NCS
			Etc					
	Etc							

*Outside the visit window

CS=Clinically Significant; NCS=Non Clinically Significant

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16 APPENDICES

16.1 STUDY FLOWCHART

	Screening Period		Study Treatment Period					Follow-up Period
	D-30 to D-1	D0	D7	D14	D28	D56	D84	D105
		W0	**W1**	**W2**	**W4**	**W8**	**W12**	**W15**
Time Window (time between two visits≤30 days)			± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days
	Screening	**Baseline**	**V1**	**V2**	**V3**	**V4**	**V5**	**EOS**
Obtained Inform Consent	X							
Check of IN/EX Criteria	X							
Medical History	X							
Height Measurement (cm)	X							
Body Weight (kg)	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
ECG (12 lead)	X	X					X	X*
Blood Pregnancy test (WOCBP)	X				X	X	X	X
Urine Pregnancy test (WOCBP)		X						
Randomization		X						
ABX464/placebo treatment dispensation		X			X	X		
Hematology + Biochemistry#	X#	X	X	X	X	X	X	X
Blood samples drug PK (pre-dose)				X		X		X**
Blood samples drug PK (1- , 2- & 3- hours post-dose)		X		X		X		
Blood samples for Cytokines (gel tube)		X	X	X	X	X	X	
Blood samples for Cytokines (Truculture® tube**)**		X				X		
Blood samples for flow cytometry cells count* **		X				X		
Blood samples for CRP, ESR	X	X	X	X	X	X	X	
Blood samples for miR-124 (Paxgene® tube)		X				X		
Tender Joint Count (28)	X	X		X	X	X	X	
Swollen Joint Count (28)	X	X		X	X	X	X	
Patient Global Assessment of Disease (PtGA-VAS)	X	X		X	X	X	X	
Patient assessment of Joint Pain (Pain-VAS)		X		X	X	X	X	
Investigator Global Assessment of Disease (PrGA-VAS)		X		X	X	X	X	
Health Assessment Questionnaire – Disease Index (HAQ-DI)		X		X	X	X	X	
Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue		X		X	X	X	X	
Patient diary (dispensation/check)		X	X	X	X	X	X	
Adverse Events recording	X	X	X	X	X	X	X	X
Follow_up Headache Questionnaire in case of persistent headache (see section 5.3.2)		X (throughout the study, if needed)						
Dermatologist consultation in case of skin effect (see section 5.3.2)		X (throughout the study, if needed)						

#Tests of TB, HIV, HCV, HBV only at screening; *ECG at EOS visit in case of early termination only; **trough levels PK samples; ***Only in French Coordinating Investigator's Site; Two visits should not be conducted more than 30 days apart