CLINICAL STUDY PROTOCOL
ABX464-301

Sponsor:	ABIVAX 5, rue de la Baume 75008 Paris FRANCE
Investigational product:	Not Available
Product code:	ABX464
Therapeutic indication:	Phase IIa 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.
EudraCT number:	2018- 004677-27
Study code:	ABX464-301
Version number:	4.0
Release date:	October 24th, 2019

CLINICAL STUDY PROTOCOL

Study code	ABX464-301
Investigational product code	ABX464
EudraCT number	2018- 004677-27
Detailed Title	Phase IIa 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.
Study Phase	Phase IIa
Coordinating Investigator	**Dr Claire DAIEN** Département de Rhumatologie Hôpital Lapeyronie ; CHU de Montpellier 34295 MONTPELLIER cedex 5 – France Tel: +33 (0) 4 67 33 87 10
Sponsor	**ABIVAX** 5 rue de la Baume 75008 Paris - France Tel: +33 (0) 1 53 83 08 41 Fax: +33 (0) 1 53 83 07 48
Date/Version	October 24th, 2019 / Version 4.0

CONTACTS

Sponsor	**ABIVAX** 5 rue de la Baume 75008 PARIS - France **Dr Jean-Marc STEENS** VP, Chief Medical Officer Tel: + 33 (0) 1 53 83 09 61 **Dr Paul GINESTE** VP, Clinical Operations Tel: + 33 (0) 1 53 83 09 61
Coordinating investigator	**Dr Claire DAIEN** Département de Rhumatologie Hôpital Lapeyronie ; CHU de Montpellier 34295 MONTPELLIER cedex 5 – France Tel: +33 (0) 4 67 33 87 10
Study Conduct, Data management and Statistical Analysis	**Simbec-Orion** Centre d'Affaires La Boursidière Bâtiment le Jura, BP 141 92357 Le Plessis- Robinson Cedex France
Pharmacokinetics	**Atlanbio (Bioanalyses)** ZI de Brais 1 Rue Graham Bell BP 40309 44605 Saint-Nazaire – France
Pharmacovigilance	**IntuVigilance Limited** Scotsbridge House, Scots Hill Rickmansworth WD3 3BB Hertfordshire, UK

INVESTIGATOR AGREEMENT PAGE

EudraCT number 2018- 004677-27

Detailed Title: Phase IIa 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.

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

- To conduct the study as outlined in the protocol, any mutually agreed future protocol amendments and with all the terms and conditions set out by ABIVAX.
- Not to implement any changes in the procedures described in the protocol without the prior approval of the sponsor and prior to review and written approval by the Ethics Committee and/or Regulatory Authorities, unless instructed otherwise by the Regulatory Authorities or the wellbeing of patients is jeopardized.
- To conduct the study in accordance with the Good Clinical Practice ICH E6 (R2) guidelines, US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations), the European Union Clinical Trials Directive 2005/28/EC, the provisions of the Helsinki Declaration, and relevant legislation in force.
- I am thoroughly aware of the study drug specifications and adverse events as described in the protocol and the current Investigator's Brochure and any other information provided by the Sponsor.
- To ensure that sub-investigator(s) and other relevant members of my staff involved in the study are fully aware of their responsibilities regarding this study and will conduct the study according to the protocol.

Investigator's Name: _____

Investigator's Signature: _____

Date: _____

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation or Term	Definition
Ab	Antibodies
ABX	Abivax
Ag	Antigens
ACPA	Anti-Citrullinated Peptide Antibody
ACR	American College of Rheumatology
AE	adverse event
IA	Intra-articular
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvate transaminase
Anti-TNFα therapy	Anti-tumor necrosis factor alpha therapy
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC0-24	area under the plasma concentration-versus-time curve from zero to 24 hours
AUC0-∞	area under the plasma concentration-versus-time curve from zero to infinity
AUC0-t	area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration
B-HCG	Beta Human Chorionic Gonadotropin
Bid	bis in die (in Latin) twice a day
BMDM	Bone Marrow Derived Macrophages
BMI	Body Mass Index
BSL	Baseline
CBC	Cap Binding Complex
CCL2	Chemokine Ligand 2
CDAI	Clinical Disease Activity Index
CFR	Code of Federal Regulations
CIA	Collagen Induced Arthritis
CI	Confidence Interval
Cmax	peak plasma concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CRF	Case Report Form
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTC-AE	Common Terminology Criteria for Adverse Events, version 5.0
CTLA	Cytotoxic T Lymphocyte Associated (molecule)
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome
DAS	Disease Activity Score
DLT	Dose Limiting Toxicity
DMARD (cs/b/ts)	Disease-Modifying Anti-Rheumatoid Drugs (conventional/biologic/targeted)
DNA	Deoxyribonucleic Acid
DBP	Diastolic Blood Pressure
DSMB	Data and Safety Monitoring Board
DSS	Dextran Sodium Sulfate
EC	European Commission
ECG	electrocardiogram
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
EOS	End of Study
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy- Fatigue
FAS	Full Analysis
FIH	First in Human
FU	Follow-up
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practice
GM	Geometric Mean
GMP	Good Manufacturing Practice
H	hours
HAQ-DI	Healthy Assessment Questionnaire-Disability Index
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	heart rate
IA	Intra Articular
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICF	informed consent form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IR	Inadequate Response
IRB	Institutional Review Board
IUD	Intra-Uterine Device
JAK	Janus Kinase
LDA	Low Disease Activity
LDH	Lactate Dehydrogenase
LPS	Lipopolysaccharide
Max	maximum
MC	Methyl Cellulose
MCP	Metacarpophalangeal (joint)
MCP-1	monocyte chemo attractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
mg	milligram
Min	minimum
miR	micro-RNA
mL	milliliter
mmHg	millimeters of mercury
MMS	Modified Mayo Score
NOAEL	No Observed Adverse Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug

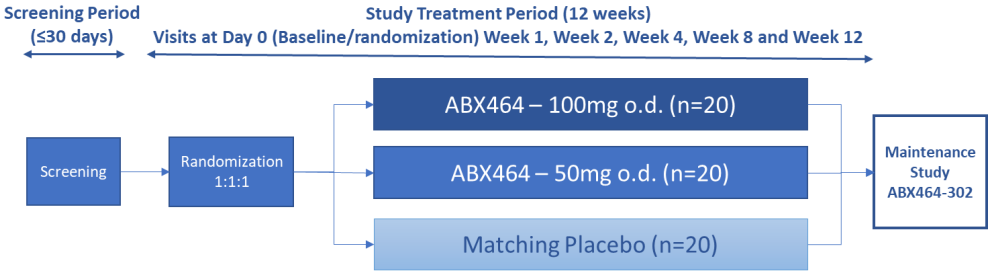
o.d.	Once Daily
PBMC	Peripheral Blood Mononuclear Cell
PCSA	potentially clinically significant abnormalities
PD	pharmacodynamics
PIP	Proximal interphalangeal (joint)
PK	pharmacokinetics
pMMS	Partial Modified Mayo Score
PP	Per Protocol
PT	Preferred Term
PtGA	Patient Global Assessment
PrGA	Provider Global Assessment
qd	Quaque die (in Latin), once a day
QTc	heart-rate–corrected QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) using Bazett's formula
QTcF	heart-rate–corrected QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) using Fridericia formula
R	Accumulation ratio
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RHI	Robarts Histopathology Index
RNA	Ribonucleic Acid
SAF	Safety
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SCR	Screening
SD	standard deviation
SDAI	Simplified Disease Activity Index
SEM	standard error of the mean
SF-36	Quality of Life Questionnaire
SJC	Swollen Joint Count
SLE	Systemic Lupus Erythematous
SOC	system organ class
STAT3	Signal Transducer and Activator of Transcription 3
t1/2	terminal half-life
TB	Tuberculosis
TEAE	treatment emergent adverse event
TJC	Tender/painful Joint Count
tmax	time to peak plasma concentration
TMS	Total Mayo Score
TNFα	Tumor Necrosis Factor alpha
TREX	Transcription/export complex
UC	Ulcerative Colitis
ULN	Upper Limit Normal
VAS	Visual Analog Scale
Vd/F	volume of distribution
vs	versus
WOCBP	Women of Child Bearing Potential

SYNOPSIS

<table>
<tr><td colspan="2">Study n° ABX464-301 Clinical Phase IIa
Type of Study Safety, Tolerability, Efficacy Study</td></tr>
<tr><td>Study title</td><td>Phase IIa 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.</td></tr>
<tr><td>Short title</td><td>Phase IIa study of ABX464 in moderate to severe active Rheumatoid Arthritis patients.</td></tr>
<tr><td>Investigators and study centers</td><td>Approximately 20 sites in Europe will participate in this study</td></tr>
<tr><td>Study Duration</td><td>Recruitment period: Q2 2019 – Q2 2020
Overall Study period: Q2 2019 – Q4 2020</td></tr>
<tr><td>Investigational product</td><td>ABX464 is a small molecule that binds the Cap Binding Complex (CBC), a protein complex sitting at the 5’ ends of RNAs and that is involved in cellular RNA integrity (e.g. splicing). ABX464 does not affect RNA biogenesis from cellular genes. ABX464 enhances the splicing of a long non-coding RNA to up-regulate microRNA miR-124, which functions as a potent endogenous anti-inflammatory mediator. ABX464 has anti-inflammatory properties in dextran sulfate sodium (DSS) induced colitis mice model and collagen induced arthritis mice model. Administration of ABX464 has demonstrated clinical efficacy in moderate to severe Ulcerative Colitis (UC) patients. ABX464 was safe and well tolerated in approximately 200 volunteers and patients in phase I and II clinical trials.</td></tr>
<tr><td>Study Design and Methodology</td><td>This Phase IIa study aims at investigating the safety and tolerability of 2 dose-levels of ABX464 administered daily in combination with methotrexate (MTX) in patients with moderate to severe active Rheumatoid Arthritis (RA) who had an inadequate response to MTX or/and to one or more anti- tumor necrosis factor alpha (TNFα) therapies.

In addition, 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.
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.
Eligible patients will be randomized, according to a 1:1:1 ratio into 3 parallel intervention/treatment groups:
<table>
<tr><th></th><th>Intervention/treatment Active Arm</th></tr>
<tr><td>Group #1 (n=20): 100mg qd</td><td>2 capsules of 50mg ABX464</td></tr>
<tr><td>Group #2 (n=20): 50mg qd</td><td>1 capsule of 50mg ABX464 + 1 capsule of matching placebo</td></tr>
<tr><td>Group #3 (n=20): Placebo</td><td>2 capsules of matching Placebo</td></tr>
</table>
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 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) of treatment.
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</td></tr>
</table>

Study n° ABX464-301	**Clinical Phase** IIa **Type of Study** Safety, Tolerability, Efficacy Study
	approvals. In the present study (ABX464-301), 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 therapy. Study scheme: 
Study Objectives	**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. **Secondary Objectives** The secondary objectives are: ▪ 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 Outcomes (PRO), Healthy Assessment Questionnaire – Disability Index (HAQ-DI) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue; ▪ To evaluate the expression of miR-124 in total blood (determined by qPCR) at baseline and Week 8 ▪ To evaluate the effect of the 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.
Study Endpoints	Primary Safety Endpoint: ▪ Incidence of treatment-emergent adverse events in the ABX464 treated Patients versus placebo, categorized by severity Secondary Endpoints: *Main 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),

Study n° ABX464-301	**Clinical Phase** IIa **Type of Study** Safety, Tolerability, Efficacy Study
	○ Disability index of the healthy assessment questionnaire (HAQ-DI) *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; ○ 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.
Main Selection Criteria	**Inclusion criteria:** **A patient will be eligible to participate in this study if ALL the following criteria are met:** ▪ Men or women age 18 - 75 years; ▪ 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 (SJC) of ≥ 4 (28-joint count) and tender joint count (TJC) ≥4 (28-joint count) at screening; ▪ Patient with a moderate to severe disease activity score DAS28 CRP ≥ 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.

Study n° ABX464-301	**Clinical Phase**	IIa
	Type of Study	Safety, Tolerability, Efficacy Study

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.

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

Study n° ABX464-301	**Clinical Phase** IIa **Type of Study** Safety, Tolerability, Efficacy Study
	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.
Medications	**Mandatory Medications:** ▪ ABX464 or its matching placebo administered once daily; ▪ MTX ≥ 10 mg/week, at previous dose regimen kept stable 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. **Potential Drug-Drug Interactions (DDIs) with methotrexate:** ABX464 is mainly metabolized by CYP1A2 and glucuro-conjugated. Methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms. Multiple DDIs have been documented with methotrexate. In this study, potential methotrexate interactions on ABX464 will be sought using an on-going PK modelling approach. For documented DDIs with methotrexate, please refer to the Appendix 5. **Allowed Concomitant Medications:** ▪ 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. **Prohibited Concomitant Medications:** ▪ 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.
Premature trial discontinuation	Patient's premature trial discontinuation must occur for the following reasons: ▪ Investigator's decision; ▪ An Adverse Event or an intercurrent condition that preclude continuation of treatment;

Study n° ABX464-301	**Clinical Phase** IIa **Type of Study** Safety, Tolerability, Efficacy Study
	○ Specifically, an increase ≥ 3.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or an increase ≥ 2.0 x ULN in Alkaline phosphatase or in total bilirubin requires close observation with repeating liver enzymes and serum bilirubin tests two times weekly and clinical investigation to understand the etiology of this elevation. Frequency of retesting can decrease to once a month if abnormality stabilizes after this initial two weeks of follow-up and if the patient is asymptomatic. Discontinuation of the study treatment should occur if: • ALT or AST > 8xULN • ALT or AST >5xULN for more than 2 weeks • ALT or AST > 3xULN and total bilirubin > 2xULN or INR>1.5 • ALT or AST > 3xULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). ▪ Worsening of the RA (according to physician evaluation); ▪ Major protocol violation; ▪ Withdrawal of consent; ▪ Administrative reasons from Sponsor.
Patient Follow-up	On 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.
Data Safety Monitoring Board (DSMB)	A Data Safety Monitoring Board with expertise and experience in the management of Rheumatoid Arthritis will review the safety of the trial. The DSMB will meet after the first 6 patients (i.e. 50mg) are dosed 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.
Sample Size calculation	The primary efficacy endpoint is the ACR20 response rate of subjects. This response rate will be compared in subjects who received ABX464 or placebo by likelihood ratio chi-square test. For the sample size assessment, the following assumptions will be made: • Response rate (ABX464): 0.65 • Response rate (placebo): 0.25 • Type 1 error: 10% two-sided • Group allocation rate (ABX464 100mg / ABX464 50mg / 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.
Statistical Methods	**Safety:** Analysis of safety will be performed on the safety data set consisting in all subjects who received at least one dose of ABX464 in the study. Primary safety endpoint, the rate of all treatment emergent adverse experiences, will be compared in subjects who received a given dose of ABX464 or placebo by likelihood ratio chi-square test on a 10% two-sided significance level. Further assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the "CTC-AE" (Version 5.0) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and PCSAs [potentially clinically significant abnormalities (PCSAs) determined upon investigator considerations]. Adverse events will be tabulated (counts and percents) by group. All adverse events will be listed, and the data will be tabulated by body system/organ class. Adverse event tabulations will include all treatment emergent adverse events, which will be further classified by severity, and relationship to treatment. Clinical laboratory parameters, vital signs, ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Number of subjects with at

Study n° ABX464-301	**Clinical Phase** IIa **Type of Study** Safety, Tolerability, Efficacy Study
	least one abnormal value will be tabulated (counts and percents) for each parameter in summary shift tables by group**.** **Efficacy:** Analysis of efficacy data will be carried out in the Full Analysis Set in which subjects who prematurely terminate the study will be considered failures. The primary efficacy endpoint of the study, the 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. The result of the test will be interpreted in a descriptive manner therefore no adjustment for the multiple comparison is applied. In addition, descriptive statistics will be presented by treatment arm for all secondary efficacy variables for each measurement timepoints separately for the two study groups. These statistics include: o Continuous variables: mean, standard deviation, minimum and maximum, stratified 95% confidence intervals, median and quartiles will be presented. o 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: o The change from baseline in DAS28-CRP and DAS28-ESR o 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 o The change from baseline in SDAI and CDAI scores o The change from baseline in miR-124 in total blood at Week 8 In this model, treatment will be fixed effect, 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. **Pharmacokinetics:** Even though the PK characteristics of ABX464 are well documented in healthy volunteers and HIV-infected subjects, the RA condition deserves a population PK exploration. Hence, PK determinations will be performed in subjects enrolled in this study. The PK evaluation consists of pre-dose samples on Week 2 and Week 8, 1-, 2- and 3-h post-dose samples on Baseline, Week 2 and Week 8, and trough-dose sample on EOS visit. The following PK parameters will be derived for ABX464, NGlcABX464 for each subject: o Cmax, tmax: the maximum plasma concentration (Cmax) and the time taken to reach Cmax (tmax) will be obtained directly from the concentration-time data. o $AUC_{0-\tau}$: the area under the concentration-time curve from time zero to the time of dosing interval τ (12 h post-dose for ABX464 and NGlcABX464). If no concentration can be measured at this time point, AUC0-last (from time zero to the last quantifiable concentration) will be calculated. Both parameters will be presented independently. For both parameters, a linear trapezoidal method will be used

1. INTRODUCTION AND STUDY RATIONALE

1.1. Rheumatoid Arthritis (RA)

1.1.1. Disease

Rheumatoid arthritis (RA) is the most common auto-immune inflammatory arthritis in adults, characterized by a progressive functional impairment (1). RA has a significant negative impact on the ability to perform daily activities, including work and household tasks, and health- related quality of life, and it increases mortality (2,3).

1.1.2. Management of patients

The treatment of RA consists of an integrated approach that includes pharmacologic and non-pharmacologic therapies, including exercise, diet, massage, counseling, stress reduction, physical therapy and surgery. Active participation of the patient and the family in the design and implementation of the therapeutic program helps boost morale and ensure compliance (4).

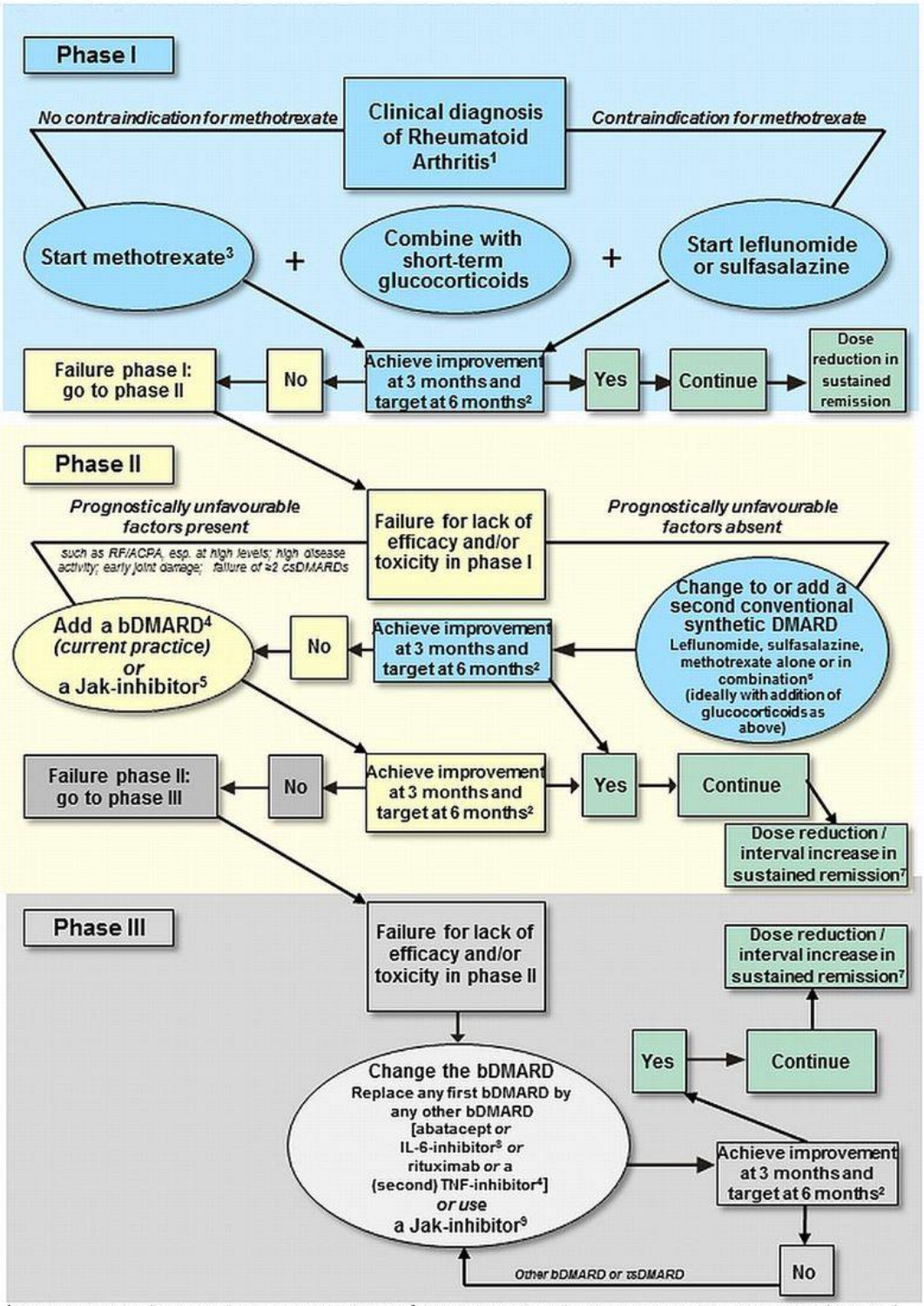
Arthritis medication plays an essential role in controlling the progression and symptoms of RA (joint damage, pain, stiffness, inflammation and complications). The treatment will depend of the stage of the disease.

The 2015 American College of Rheumatology and the 2016 EULAR guidelines recommends for the treatment of RA the use of methotrexate (MTX), or in case of contra-indication, the use of another conventional disease-modifying antirheumatic drugs (cDMARDs), including hydroxychloroquine, leflunomide, and sulfasalazine (5,6).

Low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) could be added in patients with moderate or high RA disease activity or during RA disease flares. Analgesics, such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) might relieve symptoms such as pain and stiffness (4).

If disease activity remains moderate or high despite DMARD monotherapy, either other csDMARD therapy might be used or a biologic DMARD (bDMARD), such as anti-Tumor Necrosis Factor (TNF) therapies (infliximab, etanercept, adalimumab, certolizumab or golimumab), non-TNF biologic DMARDs (abatacept, tocilizumab, sarilumab or rituximab in certain circumstances) or a Janus-Kinase (JAK) inhibitor (baricitinib, tofacitinib) might be used, preferentially in combination with MTX.

If the disease activity remains moderate or high despite the use of targeted therapy (b or tsDMARD), a switch to another targeted therapy will be proposed, preferentially in combination with MTX (5, 6).



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

Figure 1: Algorithm based on the 2016 EULAR recommendation on RA management (6)

A failure to respond to anti-TNF therapies remains a serious concern for patients with RA. Although some patients experience a primary lack of drug efficacy in reducing their symptoms, others fail to maintain an initial response because of acquired drug resistance. Switching to another anti-TNF therapy is a common practice for patients who are not responsive. However, if more than one anti-TNF therapy has provided inadequate response and/or similar tolerability issues, switching to a different class of agent, with a mechanism of action unrelated to TNF inhibition, may provide a more effective option (7).

1.2. ABX464 rationale

1.2.1. Investigational treatment description

ABX464 is a first in class and unique small molecule that has demonstrated an anti-HIV effects and anti-inflammatory properties in several pre-clinical models and in patients.

ABX464 was shown to be able to reduce the viral load in a transgenic mice model during treatment period. This viral load reduction was maintained after ABX464 discontinuation demonstrating a long-lasting effect. ABX464 was also shown to be effective on all clinical HIV strains tested and did not induce any resistance up to 24 Weeks of treatment. Therefore, ABX464 is being developed throughout Phase IIa studies in patients infected by the HIV.

Besides its antiviral indication (HIV), *in-vitro* assays revealed that both ABX464 and its primary metabolite, N-Glu-ABX464, induced a significant increase in miR-124 expression in PBMCs and up-regulated a cytokine (IL-22) in LPS-stimulated BMDMs (Bone Marrow Derived Macrophages).

MiR-124 is known for its anti-inflammatory effects. Reduced levels of miR-124 in colon tissues of children with active UC appear to increase expression and activity of STAT3, which could promote inflammation and pathogenesis of UC in children [7]. In addition, IL-22 is a key cytokine in intestinal inflammation recovery [8].

These findings suggest that the modulation of miR-124 by ABX464 led to study disease specific anti-inflammatory effects.

1.2.2. Investigational product description

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

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

1.2.3. Investigational product Mode of Action

HIV Indication:

Alternative splicing is a key event for HIV replication. Successful infection and production of new infectious viruses requires the balanced expression of seven additional viral proteins (Rev, Tat, Nef, Vif, Vpr, Vpu and Env) that are produced by splicing of the primary 9 kb transcripts among which the Tat and the Rev factors are absolutely required for viral gene expression at the transcriptional and post-transcriptional levels in infected cells. While most cellular unspliced RNAs are retained in the nucleus where they are degraded, nuclear export of the unspliced viral RNAs is facilitated by the Rev protein, through binding to a viral sequence called the rev responsive element (RRE). Both RNA export and RNA splicing are controlled by the cap binding complex (CBC) which interacts directly with either Rev or the transcription/export (TREX) complex, a multiprotein complex, required for transcription and export of bulk mRNAs. These interactions are thought to recruit Rev and TREX to a region near the 5′-terminal cap structure of mRNA and thereby connect the transcription and export of newly transcribed RNAs.

ABX464 by binding directly to CBC, specifically prevent Rev-mediated splicing and export of viral RNA without interfering with cap binding or export of cellular transcripts.

UC indication

The mechanism of action of ABX464 in UC is mediated throughout the observed effect on miR-124 observed in vitro and in patients. ABX464 in a DSS mice model has no effect on the expression profile of cytokines and chemokine signaling pathways in the absence of DSS exposure. Interestingly, in presence of dextran sodium sulfate (DSS), ABX464 compensated for most of the expression differences

induced by DSS exposure, which suggests that ABX464 restores the transcriptional program modified by DSS in the colon. In addition, in the DSS model, ABX464 leads to reduced expression of pro-inflammatory cytokines: IL-6 (2x), TNF (7.5x) and MCP-1 (6x).

1.2.4. Rationale for the development of ABX464 in Rheumatoid Arthritis

In-Vitro assays

- *Modulation of miR-124 by ABX464*

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

- *Bone Marrow Derived Macrophages – LPS Challenge*

Stimulation of BMDMs with LPS induced the expression of IL6, TNFα, and MCP1 (CCL2) but not that of IL10 (Figure 2B). The expressions of MCP1 and IL6 persisted for 48 h post LPS-stimulation, whereas TNF expression was down-regulated at 12 h (Figure 2B). Strikingly, ABX464-exposed BMDMs displayed an increased production of IL-10 at 12 and 24 h post LPS-stimulation but did not alter levels of the pro-inflammatory cytokines IL6 and TNFα (Figure 2B).

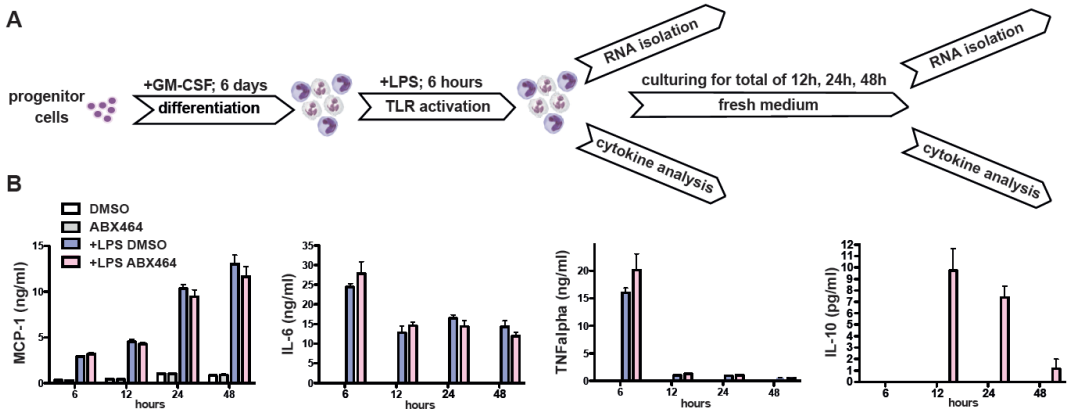


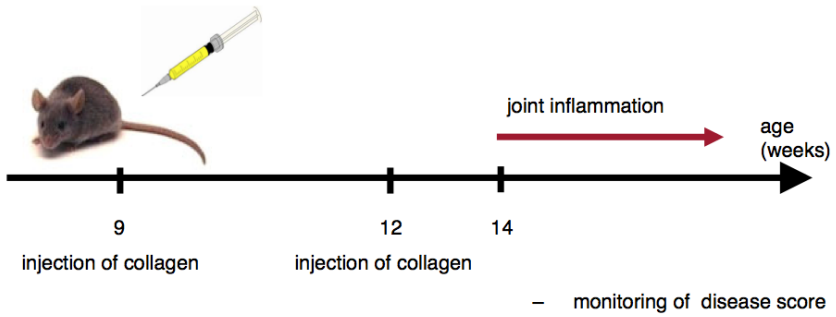
Figure 2. Effect of ABX464 on cytokine secretion (A) Bone marrow isolated cells were cultured for 6 days in the presence of GM-CSF (50ng/ml) to differentiate into macrophages. Cells were kept in culture for additional 3 days in the presence of ABX464 (5µM) or vehicle (DMSO) alone and for additional 6 hours stimulated with LPS (4µg/ml). Cells were then kept in normal medium for additional 42 hours. Cell aliquots for RNA isolation and supernatants were taken at time 6, 12, 24 and 48 hours. **(B)** Culture supernatants of the indicated cell cultures were analyzed by CBA for the content of MCP-1, IL-6, TNFalpha and IL-10.

In-Vivo assays

- **Collagen induced arthritis mouse model**

The Collagen Induced Arthritis (CIA) protocol induces Arthritis in DBA1 mice.

Collagen induced arthritis (CIA)



In this model, the inflammation is characterized by persistent joint swelling and progressive destruction of cartilage and bone.

To test the protective effect of ABX464, the compound was suspended in methylcellulose (MC 0,5/100) and administered daily from week 12 via gavage (per os).

In experiment 1: Named “DBA-1”

- Mice were treated as follow (10 animals per cohort were distributed in two cages):
- Cohort 1: 10 male mice gavage ABX464 40mg/Kg
- Cohort 2: 9 male mice gavage MC (carrier)
- Cohort 3: 6 female mice gavage MC (carrier)

In experiment 2: Named “DBA-2”

- Cohort 1: 10 male mice gavage ABX464 40mg/Kg
- Cohort 2: 10 male mice gavage MC (carrier)
- Cohort 3: 10 male mice gavage H2O

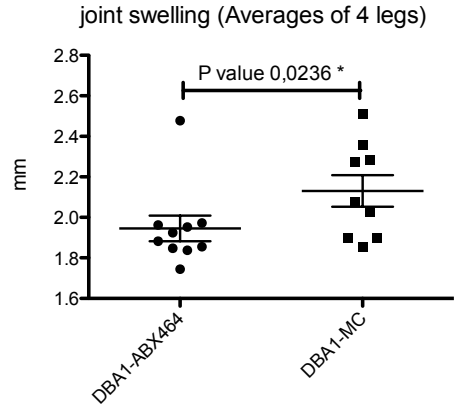
In these two experiments, DBA-1 & 2, cohort 1 & 2 were repetition of sampling in two independent experiments. In experiment DBA-1, cohort 3 tested if females are equally sensible to induction of CIA.

In Experiment DBA-2, cohort 3 received a water gavage per os in place of MC to test if the water retention of the MC modified the result.

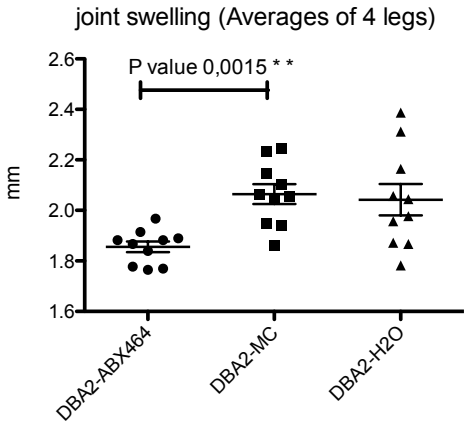
Mice were examined visually for the appearance of arthritis in the peripheral joints and disease severity was graded. Mice were considered to have arthritis when significant changes in swelling were noted in the digits & limb.

The swelling was measured, and a value of inflation was measured for every limb and the average was made. The exact average of joint swelling week 21 is indicated for each of both independent experiment on the graph following for each of the animal on MC and ABX464 and the P value was notified.

DBA-1 model



DBA-2 model



Number of animals with arthritis	Without ABX464	With ABX464
First Experiment (male)	7 / 9	2 / 10
Second Experiment (male)	8 / 10	1 / 10

In this study, a specific effect of ABX464 was found on Collagen Induced Arthritis (CIA). The daily contribution of 40mg/Kg of ABX464 given “per-os” allowed to reduce significantly the inflammation noticed by joint swelling, with two independents experiments, in this model.

1.2.5.Preclinical data of ABX464

1.2.5.1. Non-clinical background information

ABIVAX conducted a large pre-clinical toxicology program with ABX464. This program includes five different animal species (i.e. cynomolgus and marmoset monkeys, rats, beagle dogs and mini-pigs).

In the rat, 4-Week and 13-Week GLP repeated dose-studies were performed. In the 4-Week repeated dose-study ABX464 was overall well tolerated, transient and minor histological alterations were noted in the stomach for the highest dose-levels of 150 and 250 mg/kg b.i.d. The NOAEL was considered to be 55 mg/kg b.i.d for 28 days. In the 13-Week repeated dose-study, no adverse findings related to ABX464 treatment were observed up to the highest dose of 120 mg/kg o.d., the NOAEL was considered to be 120 mg/kg o.d. for 13 Weeks.

In non-human primates, ABX464 oral treatment induced frequent vomiting, body weight loss and gastrointestinal inflammation for dose-levels of 75 mg/kg b.i.d. and above. The main target organs of ABX464 toxicity were found to be those of the gastro-intestinal tract. The NOAEL was considered to be below 75 mg/kg b.i.d. Treatment of marmoset monkeys with ABX464-N-Glu induced premature death at the intermediate dose of 300 mg/kg and the high dose of 1000 mg/kg. Although the death of 2/3 animals was attributed to misgavage, additional toxicities were observed and included respiratory and gastro-intestinal tract signs and a decrease in spontaneous locomotor activity.

In the dog, ABX464 oral treatment induced digestive effects, body weight losses, impaired food consumption and decreased red blood cell parameters for dose levels of 20 mg/kg o.d. and above. The NOAEL was considered to be 20 mg/kg o.d. in males and 5 mg/kg o.d. in females.

In the minipig, in the 14-day study, ABX464 oral treatment induced a reduced food intake associated with body weight loss for dose levels of 10 mg/kg o.d and above, which resolved after termination of treatment. In the 3-month study, ABX464 at dose levels of 5, 10 and 15 mg/kg o.d. was well tolerated since no findings of toxicological importance were described. However, toxic effects appeared shortly before completion of the third month of treatment in the 26/39 Weeks study in minipigs at the same dose-levels. The main adverse finding was centrilobular hepatocellular degeneration/necrosis associated with hemorrhage, fibrosis and /or extramedullary hematopoiesis observed at dose levels of 10 mg/kg and above. The liver lesions observed in the single animal administered 5 mg/kg o.d. were not considered adverse. Based on this observation, the NOAEL was considered to be 5 mg/kg o.d.

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

Reprotoxicity assessed from fertility to postnatal development, was explored in five studies. In rabbits, the maternal NOAEL was considered to be 9 mg/kg o.d. and the NOAEL for the embryo-fetal development less than 1 mg/kg o.d. In rats, the maternal NOAEL and the NOAEL for pup development and survival is considered to be lower than 15 mg/kg o.d.. The F1 generation NOAEL is considered to be 40 mg/kg o.d. in absence of adverse effect at this dose-level.

It is likely that ABX464 has teratogenic activity and the main target organs of ABX464 toxicity were found to be the gastro-intestinal tract and the liver.

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

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

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

1.2.6.Previous clinical experience with ABX464

A First In Human (FIH), Single dose, dose-escalating exploratory study evaluating ABX464 administered at 50, 100, 150 or 200mg to healthy male volunteers has been completed. Pharmacokinetic data collected in this study showed that ABX464 is substantially metabolized into the ABX464-N-glucuronide. ABX464's Cmax was observed approximately 2 hours after dosing in all groups, with mean values ranging from 14 to 72 ng/mL. ABX464-N-glucuronide's Cmax was about 160-fold higher. The limit of exposure was reached at 150 mg. No serious adverse events were reported during the study. Thirteen (13) patients experienced mild to moderate headache, nausea and/or vomiting. No clinically significant abnormal results were noted in physical examinations, laboratory test results, vital signs and ECG.

The drug was well tolerated up to 150 mg, three out of six patients experienced vomiting at 200 mg. Nausea and headaches were reported in these patients.

A second exploratory trial (ABX464-002/ABX464-FE-001) in male healthy volunteers investigating the potential effects of food on pharmacokinetic parameters of ABX464 administered at single and repeated doses of 50 mg has been completed. No serious adverse events related to the IMP have been reported. The main adverse events recorded were headache, nausea and vomiting. A significant increase in ABX464 exposure was observed in the fed group and no significant impact on ABX464 metabolism was noted. ABX464 should be taken with food.

A first phase IIa (ABX464-003), dose escalation, placebo-controlled study to evaluate the safety, pharmacokinetics, and viral kinetics of ABX464 in naive patients with HIV infection has been recently completed. The objective of this study was to evaluate the safety of ABX-464 at ascending doses versus placebo in HIV-infected treatment-naive patients. Patients were randomized into successive cohorts of 8 patients where 6 received 14 or 21 days of ABX464 and 2 placebos. At day 0, patients received the first dose of ABX-464/ placebo in a once daily schedule. Safety assessments and laboratory parameters were recorded throughout the study. The only adverse events noted were nausea, vomiting, headache and upper abdominal pain. All adverse events were grade 1 or 2 and all patients completed at least 14 days of treatment.

A second multi-center, randomized, double-blind, placebo-controlled Phase IIa trial was conducted (ABX464-004). The main study objective was to compare the safety of ABX464 given at a fixed dose to placebo in fully controlled HIV infected patients treated with boosted protease inhibitor treatment (darunavir/ritonavir or darunavir/cobicistat). 50 patients received either ABX464 (50/150mg od) or its matching placebo according to a 3/1 ratio. The safety profile was good, and no serious adverse reactions were reported.

A third study in the HIV indication (ABX464-005 / Phase Ia) was conducted at a single site in Spain. Two cohorts of HIV-Infected patients dosed respectively with 150mg q.d for 28 days (n=11) and 50mg q.d for 84 days (n=13). The safety profile is good and consistent with previous studies. No serious adverse reactions have been reported.

A Proof of Concept study (ABX464-101 / phase IIa) has been carried out in 32 patients with moderate to severe Active Ulcerative Colitis who have failed or are intolerant to immunomodulators, Anti-TNFα or Corticosteroids.

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

1.3. Rationale for the clinical study and study design

This study is the first in disease proof of concept study. The study population (i.e. Subjects with moderate to severe active Rheumatoid Arthritis who have failed, had an inadequate response to methotrexate (MTX) or/and anti-TNFα therapy (or were intolerant to anti-TNFα therapy) was selected since this population consists in subjects who are at need of alternative therapy and in whom the safety profile of ABX464 can be reliably assessed.

The double-bind placebo-controlled design corresponds to a standard in this disease for which a placebo effect can be frequently observed.

2. STUDY OBJECTIVES AND ENDPOINTS

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:

- 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.

2.3. Primary Endpoint

The primary endpoint is the incidence of treatment-emergent adverse events in the ABX464 treated Patients versus placebo, categorized by severity.

2.4. Secondary Endpoints

Main 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

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.

3. INVESTIGATIONAL PLAN

3.1. Study design

3.1.1. Design and methodology

This Phase IIa study aims at investigating the safety and tolerability of 2 dose-levels of ABX464 administered daily in combination with methotrexate (MTX) in patients with moderate to severe active Rheumatoid Arthritis (RA) who had an inadequate response to MTX or/and to one or more anti- tumor necrosis factor alpha (TNFα) therapies.

In addition, 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.

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.

Eligible patients will be randomized, according to a 1:1:1 ratio into 3 parallel intervention/treatment groups:

	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

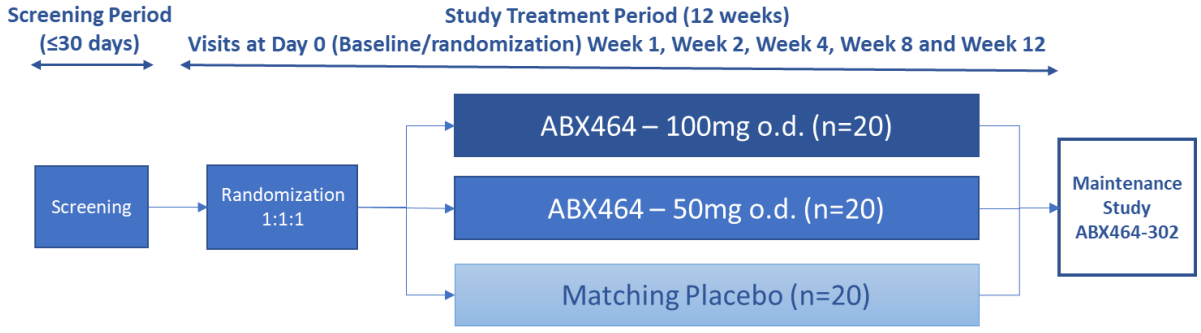
Patients will be treated for 12 weeks, followed by a follow-up period (21 days).

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:



In the present study (ABX464-301), 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

therapy.

3.1.2.Dose limiting toxicity (DLT)

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

If more than 2 DLTs occur in the first 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.

3.1.3.Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB), with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee effective protection of patients, 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.

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

3.2. Duration of study participation

Eligible patients will be enrolled in the present study at the screening visit within 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.

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 (End of Study Visit) 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.

Thus, the total duration of the study participation is approximately 15 to 19 Weeks.

4. STUDY POPULATION

4.1. Number of Patients/Centers

Up to 60 patients will be randomized in this study. These patients will be enrolled in approximately 20 sites located in Europe.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

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

- Men or women age 18 - 75 years;
- 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.

4.2.2.Exclusion Criteria

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

- 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.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1. Study Flow Chart

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

	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

5.2. Study conduct

It is the Investigator's responsibility to ensure that all the assessments are carried out during each visit and that the intervals between visits/follow-ups are adhered to.

5.2.1. Screening Visit (within 30 days prior to Baseline/Day 0)

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

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

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

- Inclusion/exclusion criteria will be verified globally, including disease confirmation according to the revised 2010 ACR-EULAR classification criteria with at least one positive criteria among the following: Rheumatoid Factor (RF), Anti-Citrullinated Peptide Antibody (ACPA) or bone erosion;
- Body weight and height;
- Medical history;
- Physical examination and vital signs;
- 12 leads ECG;
- Hematology and Biochemistry panel;
- Blood pregnancy test for all women of childbearing potential;
- Blood samples for testing TB, HIV, HCV, and HBV;
- Blood samples for acute phase reactants;
  - C-Reactive Protein (CRP)
  - Erythrocyte Sedimentation Rate (ESR)
- Tender/painful joint count (TJC) (28);
- Swollen joint count (SJC) (28);
- Patient global assessment of disease (PtGA);
- If the patient was treated by anti- TNFα therapy, confirm the adequate wash-out of the anti-TNFα therapy has started at least and collect the reason of anti- TNFα therapy discontinuation (i.e. intolerance, primary or secondary resistance):
  - 1 month prior to screening for adalimumab and etanercept
  - 2 months prior to screening for infliximab, certolizumab pegol, golimumab
- Record all medications received within 3 months prior to baseline and note if the medication is continuing; Record all RA medication without time limitation;
- Adverse Event reporting;
- Schedule next patient visits.

NB: If patient meets all eligibility criteria, has an adequate wash-out of previous therapies and laboratory results are available, the baseline visit could be performed on the same day as screening visit. In that case, it is not necessary to repeat twice the assessments required at both visits. The following additional baseline assessments have to be performed:

- Urine Pregnancy test for all women of childbearing potential;
- Pharmacokinetics blood samples at 1h-, 2h- and 3-hours post-dose;
- Patient assessment of joint pain (Pain-VAS);
- Investigator global assessment of disease (PrGA);
- Disability index of the healthy assessment questionnaire (HAQ-DI);
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- Record any concomitant medications;
- Confirm the wash-out of the anti-TNFα therapy is complete;
- Randomization;
- Dispense study treatment to patient and instruct how to take it (first dosing at site);
- Dispense patient diary (for treatment compliance and adverse event recording) and instruct how to complete it.

5.2.2. Baseline (First dosing day / Day 0)

- Physical examination and vital signs;
- Body weight;
- 12 leads ECG;
- Hematology and Biochemistry panel;
- Urine Pregnancy (β-HCG) test for all women of childbearing potential;

- Pharmacokinetics blood samples at 1h-, 2h- and 3-hours post-dose;
- Blood samples for acute phase reactants (CRP & ESR);
- Blood (gel tubes and Truculture® tubes) samples for cytokines determination;
- Blood samples (Paxgene® tubes) for miR-124 dosage;
- Blood samples for flow cytometry cells count (including at least B & T lymphocytes, myeloid cells and macrophages) (only in the Coordinating Investigator's site);
- Tender/painful joint count (28) (TJC28);
- Swollen joint count (28) (SJC28);
- Patient global assessment of disease (PtGA);
- Patient assessment of joint pain (Pain-VAS);
- Investigator global assessment of disease (PrGA);
- Disability index of the healthy assessment questionnaire (HAQ-DI);
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue;
- Record any concomitant medications;
- Confirm the wash-out of the anti-TNFα therapy is complete;
- Adverse Events reporting;
- Randomization;
- Dispense study treatment to patient and instruct how to take them (first dosing at site);
- Dispense patient diary (for treatment compliance and adverse event recording) and instruct how to complete them;
- Schedule next patient visits.

5.2.3. Week 1 / Day 7 (+/- 2 days) - Visit 1

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry;
- Blood samples for cytokines determination
- Record any concomitant medications;
- Check treatment compliance on patient diary;
- Adverse Events reporting;
- Schedule next patient visits.

5.2.4. Week 2 / Day 14 (+/- 2 days), Week 4 / Day 28 (+/- 2 days), Week 8 / Day 56 (+/- 2 days), Week 12 / Day 84 (+/- 2 days) - Visits 2, 3, 4, 5

- Physical examination and vital signs;
- Body weight;
- 12-leads ECG (D84 only);
- Hematology and Biochemistry panel;
- Blood pregnancy test for all women of childbearing potential (except on Week 2);
- Pharmacokinetics blood samples pre-dose, 1h-, 2h- and 3-hours post-dose (Week 2 / Day 14 and Week 8 / Day 56 only);
- Blood samples for acute phase reactants (CRP, ESR);
- Blood samples (gel tubes) for cytokines determination;
- Blood samples (Truculture® tubes) for cytokines determination at Week 8 only;
- Blood samples (Paxgene® tubes) for miR-124 qPCR dosage (Week 8 only);
- Blood samples for flow cytometry cells count (including at least B & T lymphocytes, myeloid cells and macrophages) (only in the French Coordinating Investigator's site, at Week 8 only);
- Tender/painful joint count (28) (TJC28);

- Swollen joint count (28) (SJC28);
- Patient global assessment of disease (PtGA);
- Patient assessment of joint pain;
- Investigator global assessment of disease (PrGA);
- Disability index of the healthy assessment questionnaire (HAQ-DI);
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue;
- Record any concomitant medications;
- Check treatment compliance on patient diary;
- Adverse Events reporting;
- Study treatment dispensation on Week 4 and Week 8 visits;
- Schedule next patient visits (time between two visits should not exceed 30 days);
- On Week 12 / Day 84, enrolment of patients willing to take part to the maintenance phase.

5.2.5. End of Study Visit (Week 15 / Day 105 ± 2 days)

This EOS visit applies to all premature discontinued patients and to patients not taking part to the maintenance study. Patients will perform an End of Study Visit (EOS) three weeks after last dosing. Patients will be treated according to the standard of care since the last day of study treatment.

Following examinations/procedures should be performed:

- Physical examination and vital signs;
- Body weight;
- Hematology and Biochemistry panel;
- Blood pregnancy test for all women of childbearing potential;
- Pharmacokinetics blood samples trough levels;
- 12 leads ECG (in case of premature discontinuation only);
- Record any concomitant medications;
- Adverse Events reporting.

NB#1: In case of premature discontinuation occurring during the treatment phase (D1-D84), the above examinations should be performed as an End of Study Visit.

5.3. Detail of the study assessments

5.3.1. Physical Examination and Vital Signs

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

Measurements of vital signs will be done at each visit (Blood pressure, Heart Rate, Body temperature). The patient should rest supine for at least 10 minutes prior to measurements. The measurements can be performed either in sitting or supine position of the patient. The right or left arm may be used. However, the position and the arm used for measurement should be kept constant throughout the trial for an individual patient.

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

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

5.3.2.Adverse Events of Interest

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

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

5.3.3. Pregnancy

For all female patients of childbearing potential, a blood pregnancy test (beta human chorionic gonadotropin [βHCG]) will be performed at Screening, on Week 4 / Day 28, Week 8 / Day 56, Week 12 / Day 84 and EOS Visit.

A urine pregnancy test will pe performed on Baseline / Day 0 in order to obtain the result before the first ABX464 administration.

In case of positive pregnancy testing, detailed procedures can be found in section 8.3.2.

5.3.4. ECG

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. Prior to the recording the patient should be at rest for at least five minutes. Resting ECG should be performed before any examinations.

The ECG printout will be reviewed by the Investigator and a signed and dated copy of the ECG will be attached to the medical file. The original ECG printouts are considered as source data and should be stored at site. If thermal paper is used, a copy of the original ECG must also be kept.

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

5.3.5.Hematology and biochemistry

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

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.

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

The Table 1 displays the clinical laboratory parameters that must be measured.

Table 1: Laboratory Tests

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

5.3.6.Pharmacokinetics

Blood samples will be collected in all patients for PK assessment.

Sampling will be performed:

- pre-dose on Week 2 / Day 14 and Week 8 / Day 56;
- 1-, 2- and 3-hours post-dose on Baseline / Day 0, Week 2 / Day 14 and Week 8 / Day 56 and
- trough levels at the End of Study Visit (Week 15 / Day 105).

The PK samples will be kept in the local laboratory, at -20°C until pick-up.

Patient data will be pooled with data obtained in previous clinical studies in order to build a population pharmacokinetic models for ABX464 and its metabolite.

5.3.7.Disease parameters

- **Laboratory disease parameters:**
  - The **acute phase reactants**, CRP and ESR, will be dosed at every visit.
  - Blood samples (on gel tubes) for serum **cytokines** determination will be kept in the local laboratory, at -80°C (or -20°C if not possible), till the end of the study.
  - Blood samples (on Truculture® tubes) for determination of **cytokines,** produced by immune cells after stimulation (incubation at 37°C for 24 hours), will be kept in the local laboratory, **at -20°C**, till the end of the study. These samples will be performed only where the incubation procedure is feasible.
  - The blood samples for **flow cytometry cells count** (including at least B & T lymphocytes, myeloid cells and macrophages) will be kept in the local laboratory, at -80°C or will be processed immediately.

The processes for samples preparation, storage and shipment will be fully defined in the laboratory manual.

- **miR-124 modulation**

ABX464 up-regulates miR-124 in PBMCs, making this micro-RNA a potentially useful future biomarker for ABX464 treatment monitoring. Determination of miRNA level in total blood will be performed in order to assess treatment effect by comparing before and after treatment for this exploratory biomarker. Assays for miRNA determination (by qPCR method) will be conducted by a specialized central laboratory.

The total blood in Paxgene® tubes will be stored at -20°C according to lab manual instructions.

- **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:

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

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

- **Simplified Disease Activity Index (SDAI)**

This other 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).

- **Clinical Disease Activity Index (CDAI)**

This other 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.

- **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

- **DAS28-ESR remission**

A remission is considered when DAS28-ESR <2.6

- **Low Disease Activity** (LDA)

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

- **SDAI remission**

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

- **CDAI remission**

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

- **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

- **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).

- **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.

- **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.

5.3.8. Summary of blood samples

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

Table 2: Blood Volume

	REQUIRED VOLUME	COLLECTION TUBE	SCR D-30	BSL D0	D7	D14	D28	D56	D84	EOS D105	TOTAL
			SCR	BL	V1	V2	V3	V4	V5	EOS	
Hematology (Hemoglobin, Hematocrit, Red Cell Count, MCV, MCHC, Platelets, White cell count with diff.)	0.5mL EDTA blood	2mL EDTA tube	2	2	2	2	2	2	2	2	16
Prothrombin time/INR and fibrinogen		2,7 mL plasma Citrate	2,7	2,7			2,7	2,7	2,7	2,7	16,2
ESR	1mL EDTA blood	2mL EDTA tube	2	2	2	2	2	2	2		14
Biochemistry panel incl CRP, βHCG and thyroid function parameters (French sites only*)	2 mL serum + 2mL*	2 x 5mL serum gel tube	5 +5*	5 +5*	5 +5*	5 +5*	5 +5*	5 +5*	5 +5*	5 +5*	40 +40*
HBsAg, anti-HBs Ab, anti-HCV Ab, anti-HIV Ab	0.75 mL serum	2.5mL serum gel tube	2,5								2,5
Quantiferon TB Gold Plus	4 mL plasma	4 x 1mL tube	4								4
Cytokines determination on serum	min 6 mL serum	2 x 5mL serum gel tube		10	10	10	10	10	10	10	70
Cytokines determination on total blood		2 x 1 mL (Truculture® tube)		2				2			4
Samples for flow cytometry cells count **		4 x 6mL EDTA tube		24**				24**			48**
Paxgene® Tube (miR-124)	5 mL total blood	2 x 2,5 mL Paxgene® tube		5				5			10
PK samples	1.0 mL serum	2mL Li-heparin tube		6 (1,2, 3h post dose)		8 (pre-dose & 1,2, 3h post dose)		8 (pre-dose & 1,2, 3h post dose)		2 (trough levels)	24
Total per visit			**18,2** +5*	**34,7** +5* +24**	**19** +5*	**27** +5*	**21,7** +5*	**36,7** +5* +24**	21,7 +5*	**21,7** +5*	**200,7** +40* + 48**

*Only in French sites; **Only in French Coordinating Investigator Site

INVESTIGATIONAL PRODUCT(S)

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

5.4. Description of investigational treatment

The study treatment that will be administrated to patients enrolled in this Phase IIa study consists of capsules containing ABX464 or its matching placebo given orally once daily for 12 weeks.

5.5. Description of investigational Product

5.5.1.Active investigational product (ABX464)

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

For the proposed clinical trial, the IMP consists of size 01 capsules containing either 50mg or 100mg of ABX464 drug substance in the form of granulate prepared with a number of common excipients (microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate and colloidal silica).

It is supplied in high-density polyethylene bottles closed with child-resistant polypropylene screw caps with induction seals.

ABX464 will be manufactured by:

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

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

CREAPHARM (EX-SODIA)
Avenue Robert Schuman
51100 REIMS Cedex
France

Storage conditions: Do not store above 30°C (86°F). Do not refrigerate or freeze.

The capsule or combination of capsules to be used depends on the dose-level to be administered as per the clinical study protocol.

5.5.2.Placebo

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

ABX464 matching placebo will be manufactured by:

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

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

CREAPHARM (EX-SODIA)
Avenue Robert Schuman
51100 REIMS Cedex
France

Storage conditions: Do not store above 30°C (86°F). Do not refrigerate or freeze.

The capsule or combination of capsules to be used depends on the dose-level to be administered as per the clinical study protocol.

5.6. Administration and Dosing

5.6.1. Administration of the investigational product

Following randomization, patients will be treated with a daily dose of either 50mg or 100mg ABX464 or will receive placebo.

Treatment groups:

	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

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

On Day 84 visit, the patient will not take the ABX464-301 study medication (last day of study medication will be on Day 83).

Patient enrolled in the ABX464-302 maintenance study will start the study medication on Day 84 (301 study)/D0 (302 study), ABX464 50mg once daily, right after the study visit.

A paper diary in which the patient should report the number of capsules taken and the intake time from baseline visit onwards, will be given to the patient at baseline.

5.6.2. Guidelines for treatment postponement and dose modifications

No intra-patient dose escalation/dose adjustment are allowed during the study.

5.7. Method of Assigning Patients to Treatment Arms

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

Eligible 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.

Randomization will be performed via a centralized treatment allocation system that will be available 24 hours-a-day, 7 days-a-week.

Study treatment monthly dispensation:

	Bottles
Group #1 (n=20): 100mg qd	2 bottles of 50mg ABX464 capsules
Group #2 (n=20): 50mg qd	1 bottle of 50mg ABX464 capsules + 1 bottle of matching placebo capsules
Group #3 (n=20): Placebo	2 bottles of matching Placebo capsules

Study treatment dispensation will be performed three times at Day 0 (30-capsule bottles; 2 bottles), at Day 28 (30-capsule bottles; 2 bottles), and at Day 56 (30-capsule bottles; 2 bottles). In all cases, subject should return his/her used and unused bottles at each study visit for a compliance check.

5.8. Blinding and breaking the study blind

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

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

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

The IWRS will require an access code/password/PIN and is only available to staff members delegated by the PI and named on the delegation log of each site.

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

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

However, as there is no antidote, it is highly unlikely that knowledge of treatment would affect the clinical management of the patient. In case of unblinding, the patient will be immediately withdrawn from the study.

5.9. Packaging

The IMP consists in hard gelatin, powder-filled capsules (size 01) containing either 50 mg or 100mg of ABX464 or placebo supplied in study specific high-density polyethylene bottles closed with child-resistant polypropylene screw caps with induction seals.

5.10. Storage

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

ABX464/Placebo capsules should not be stored above 30°C (86°F). Do not refrigerate or freeze.

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

5.11. Product Accountability

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

5.12. Prior and Concomitant Medication

5.12.1. Mandatory concomitant treatment

- 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.

Potential Drug-Drug Interactions (DDIs) with methotrexate:

ABX464 is mainly metabolized by CYP1A2 and glucuro-conjugated. Methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms.

Multiple DDIs have been documented with methotrexate. In this study, potential methotrexate interactions on ABX464 will be sought using an on-going PK modelling approach.

For documented DDIs with methotrexate, please refer to the Appendix 5.

5.12.2. Allowed Concomitant Medications

- 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.

This information should include the name of the medication (international nonproprietary name), daily dosage, duration, indication and the time of last intake before all PK samplings.

5.12.3. Prohibited concurrent medications

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

- 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.

5.13. Life Style Guidelines

No new non-pharmacological therapies should be started during the study period.

Patients should avoid changing their accustomed exercise level throughout the study. They are also encouraged to keep their diet habits constant during the study period.

6. PATIENT COMPLETION AND WITHDRAWAL

6.1. Patient Completion

Treatment with ABX464/Placebo shall continue up to Week 12/ Day 83, except if a patient fulfils a premature discontinuation criterion (defined below).

On Day 84, patient will not take ABX464-301 study medication.

On Day 84, patients willing to carry on the study treatment will be able to take part in the long-term maintenance study (ABX464-302). Patient will sign the ABX464-302 specific informed consent and will start ABX464-302 study drug administration (50mg once daily).

In any other case, patients 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 protocol subject to health authorities and ethics committee approvals.

6.2. Premature trial discontinuation

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

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

- Investigator's decision;
- An Adverse Event or an intercurrent condition that preclude continuation of treatment;
    - Specifically, an increase ≥ 3.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or an increase ≥ 2.0 x ULN in Alkaline phosphatase or in total bilirubin requires close observation with repeating liver enzymes and serum bilirubin tests two times weekly and clinical investigation to understand the etiology of this elevation. Frequency of retesting can decrease to once a month if abnormality stabilizes after this initial two weeks of follow-up and if the patient is asymptomatic. Discontinuation of the study treatment should occur if:
        - ALT or AST > 8xULN
        - ALT or AST >5xULN for more than 2 weeks
        - ALT or AST > 3xULN and total bilirubin > 2xULN or INR>1.5
        - ALT or AST > 3xULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Worsening of the RA (according to physician evaluation);
- Major protocol violation;
- Withdrawal of consent;
- Administrative reasons from Sponsor.

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

6.3. Study Discontinuation

All patients, regardless of the completion or premature discontinuation, should perform the End of Study Visit according to the study flow-chart.

6.4. Screen and Baseline Failures

All potential patients who have signed an informed consent and are screened for enrolment in this study will be listed on the patient Screening Log/Identification List. Reasons for exclusion will be recorded for potential patients who do not enter the study.

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

A patient will be considered a baseline failure if the patient signs the informed consent, is eligible for randomization but withdraws before the baseline visit.

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

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

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

During the screening period, only adverse event related to the screening procedures will be collected.

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

7.1. Definition of an AE

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

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

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

7.2. Definition of a SAE

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

a) Results in death

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

b) Is life-threatening

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

c) Requires hospitalization or prolongation of existing hospitalization

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

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

d) Results in persistent or significant disability/incapacity,

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

e) Is a congenital anomaly/birth defect

f) Is another medically important condition: This refers to an AE that may not be immediately life-threatening or results in death or hospitalization but may jeopardize the patient or may require

intervention to prevent one of the outcomes listed above. Based on medical and scientific judgment this should usually be considered serious.

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

7.2.1. Events and/or Outcomes Not Qualifying as SAEs

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

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

7.3. Events or Outcomes Qualifying as AEs or SAEs

7.3.1. Clinical laboratory parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g. vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definitions of sections 7.1 and 7.2 respectively. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at informed consent and significantly worsen during the study will be reported as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied and are present at the start of the study but do not worsen, will **not** be reported as AEs or SAEs. However, if these findings or assessments are judged by the investigator to be more severe than expected considering the patient's condition, then they may be reported as AEs or SAEs.

7.3.2. Pregnancy report

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

The investigator will collect pregnancy information on any woman patient or partner of a male patient, who becomes pregnant and their partner while participating in this study. The investigator will record pregnancy information on a specific pregnancy notification form and submit it to IntuVigilance Limited (see contact details in section 8.4) within 24 hours after knowledge of a patient's or partner's pregnancy. The patient or partner will also be followed to determine the outcome of the pregnancy, be it full-term or prematurely terminated. Information on the status of the mother and child will be forwarded to IntuVigilance Limited. Follow-up will normally end 6 to 8 Weeks following the estimated delivery date.

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

The time period for collecting pregnancy information is identical to the time period for collecting AEs, as stated in Section 7.4, Time Period, Frequency, and Method of Detecting AEs and SAEs. Pregnancy information is collected from the signing of informed consent to 4 Weeks after the last dose.

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

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

Moreover, any occurrence of pregnancy within 6 months post stopping dosing must be reported.

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

IntuVigilance Limited

Scotsbridge House, Scots Hill
Rickmansworth WD3 3BB
Hertfordshire, UK

Hotline phone: +44 800 689 4129

Email Address: safety@intuvigilance.com

Fax number: +44 800 915 6753

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

7.5. Recording AEs and SAEs

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

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

The following points must be recorded for each event:

- A description of the event in medical terms, not as reported by the patient;
- Date of onset (start date);
- Date of resolution (stop date);
- The time of onset with respect to administering the investigational product;
- The severity of the sign/symptom or clinically significant abnormal laboratory value according to CTC-AE Classification Version 5.0;
- The causal relationship between the investigational product and the occurrence of each AE. This will be assessed by each investigator using clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant medications, other risk factors and the temporal relationship of the event to the investigational product will have to be considered. The causality of all AEs should be assessed by the investigator with the following question: Is there a reasonable possibility that the AE may have been caused by the investigational product? And answered "NO" (if not related) and "YES" (if related);
- Action taken regarding the investigational product:
  - No action;
  - Temporary discontinuation;
  - Permanent discontinuation;
  - Patient's outcome:
  - Recovered without sequelae / resolved without sequelae;
  - Recovered with sequelae / resolved with sequelae;
  - Recovering/Resolving;
  - On-going;
  - Fatal (for SAEs only).

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

7.6. Reporting of SAEs to ABIVAX or its designee

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

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

The study specific SAE form should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. The investigator will assess causality between

the study drug and the adverse event (AE) / serious adverse event (SAE) according to the table outlined below:

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

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

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

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

7.7. Reporting of SAEs to Regulatory Authorities

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

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

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

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

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

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

8.1. Statistical and Analytical Plans

No interim analysis is planned.

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

8.1.1. Protocol deviations

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

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

In case of major protocol deviation, the patient must not be randomized (if deviation occurs at baseline) or be discontinued from the study.

8.1.2. Definition of study analysis sets

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

- The **Safety dataset (SAF population)** is defined as those patients included in the study, who have received at least one dose of the study treatment.
- The **Full Analysis dataset (FAS population)** is defined as those patients included in the study, who have received at least one dose of the study treatment, and who have at least one baseline data.
- The **Intent-to-Treat (ITT population)** is defined as those patients randomized, regardless of whether the patient received a dose of study treatment or completed the study.
- The **Per Protocol dataset (PP population)** is defined as those patients of the FAS population without any major protocol deviation.

8.1.3. Patients/Patients disposition

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

8.1.4. Demographic and other baseline characteristics

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

8.1.5. Treatment compliance

Number of doses will be presented on the FAS population.

8.2. Efficacy Analysis

Analysis of efficacy data will be carried out in the Full Analysis Set in which subjects who prematurely terminate the study will be considered failures.

The primary efficacy endpoint of the study, the 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.

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

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

These statistics include:

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

In addition to descriptive statistics, 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
- The change from baseline in miR-124 in total blood at Week 8

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

8.3. Pharmacokinetics

Population PK data analysis will be performed via three steps:

- Data preparation and exploratory: The analysis dataset will be created and formatted according to MONOLIX or NONMEM requirement using SAS®. An exploratory analysis by visual inspection of PK profiles/dose normalized PK profiles in natural and semi-log scale will be performed in order to anticipate the type of PK model (number of compartments, linear or saturable elimination, etc)
- Population PK model development: A PopPK model consists of four basic components:
    - The structural PK model, which defines the PK parameters and describes the plasma concentration-time profiles of ABX464 and its metabolite.
    - The inter-individual variability model component, which describes the inter-individual variability of PK parameters in the population
    - The residual error model component, which describes the underlying distribution of the error in the measured concentrations.
    - The covariate model component, which describes the influence of covariates such as demographic data on PK parameters.

The search for the final model will follow the following strategy:

- Selection of the simplest structural model, which predicts the plasma concentration as a function of time and dose, based on smallest objective function and by the pattern in the residual plots. The best estimation method, the most appropriate inter-individual variability (IIV) models, and the residual error model, are identified. The resulting model is called BASE model.
- Test of influence of selected covariates.

  - Refinement of inter-individual variability model and residual error models
- Model validation: Goodness of fit plots will be assessed for each important step of model building. For the final model, a visual predictive check (an evaluation graph based on simulation) will be provided.

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

8.4. Safety Analyses

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

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

Two periods will be defined for TEAE:

- Any adverse event which occurs or worsens from first dosing to Day 84;
- Any adverse event which occurs after Day 84.

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

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

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

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

Further assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the CTC-AE 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.

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

8.5. Clinical laboratory evaluation

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

In addition, shift tables from baseline will be presented.

8.6. Determination of sample size

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 (8).

- Type 1 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.

9. STUDY CONDUCT CONSIDERATION

9.1. Regulatory and Ethical Considerations

9.1.1. General Requirements

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

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6 (R2))..
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical studies on medicinal products for human use and its guidance.
- Declaration of Helsinki and its amendments.
- EudraLex GMP guidelines Annex 13 related to shipment, storage and handling of investigational products.

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

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

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

9.1.2. Independent Ethics Committee/Institutional Review Board

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

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

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

9.1.3. Patient Informed Consent

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

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

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

9.1.4. Compensation to Patients

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

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

10. STUDY MANAGEMENT

10.1. Remote Data Entry

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

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

The eCRF used for this study is validated and fulfils the GCP ICH E6 (R2) requirements, European and FDA (21 CFR Part 11) regulations.

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

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

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

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

10.2. Data management

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

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

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

10.3. Data coding

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

10.4. Randomization

Randomization will be centrally managed. It 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.

10.5. Study Monitoring

The study will be conducted in accordance with the related topic of the ICH E6 (R2) GCP guidelines. The appointed monitor will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ABIVAX requirements. Throughout the study, the monitor will arrange visits to the study center at appropriate intervals to assess the progress of the study and review the completed eCRFs.

During the monitoring visits, the monitor will:

- Ensure that the safety and the rights of patients are being protected;
- Check that the data are authentic, accurate, and complete and discuss any inconsistencies;

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

In line with ICH E6 (R2) GCP guidelines, monitoring will include verification of data entered in the CRF against the original patient records. Therefore, for the purpose of monitoring review, direct access to all study-related site and source documents is mandatory. Data items for which the eCRF will serve as the source document will be identified, agreed upon and documented. The investigator must also ensure provision of sufficient time, space and qualified personnel for the monitoring visits.

10.6. Records Retention

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

ABIVAX will inform the investigator/institution of the required time period for retaining these records in order to be compliant with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study site, as dictated by ICH E6 (R2) Section 4.9, any institutional requirements or local laws and regulations, or ABIVAX standards/procedures; otherwise, by default the retention period will be 15 years.

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

10.7. Quality Assurance and Inspection by Authorities

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

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

10.8. Study and Site Closure

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

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

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

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

10.9. Study report and Publication

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

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

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

10.10. Ownership and Confidentiality

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

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

11. REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part I. Arthritis Rheum. 2008;58:15–25.

2. Pincus T, Callahan LF, SaleWG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum. 1984;27:864–72.

3. Salaffi F, Sarzi-Puttini P, Girolimetti R, Atzeni F, Gasparini S, Grassi W. Health-related quality of life in fibromyalgia patients: a comparison with rheumatoid arthritis patients and the general population using the SF-36 health survey. Clin Exp Rheumatol. 2009;27(Supp56):S67–74.

4. National Institute for Health and Care Excellence (NICE) guideline. Rheumatoid arthritis in adults: management. www.nice.org.uk/guidance/ng100. July 2018.

5. Singh JA, Saag KG, Bridges Jr L, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheum. 2016;68 (vol.1):1-26.

6. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann. Rheum. Dis. 2017;76:960-977

7. Emery P. Optimizing outcomes in patients with rheumatoid arthritis and an inadequate response to anti-TNF treatment. Rheumatology 2012;51:v22-v30

8. Ronald F. van Vollenhoven et al. for the ORAL Standard Investigators. Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis. N Engl J Med 2012; 367:508-519 August 9, 2012

12. APPENDICES

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

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

Appendix 2: HAQ-DI

The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pul long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Raised toilet seat
☐ Bathtub seat
☐ Jar opener (for jars previously opened)
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Long-handled appliances in bathroom

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene
☐ Reach
☐ Gripping and opening things
☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.
How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL () MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

No Pain — **Severe Pain**

0 — 100

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line.

Very Well — **Very Poor**

0 — 100

Appendix 3: Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

FACIT Fatigue Scale (Version 4)

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

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

Appendix 4: Follow_up Headache Questionnaire

Follow Up Headache Questionnaire

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

Please describe your headaches:

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

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

2. How frequent are your headaches?

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

3. How long do your headaches last in days?

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

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

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

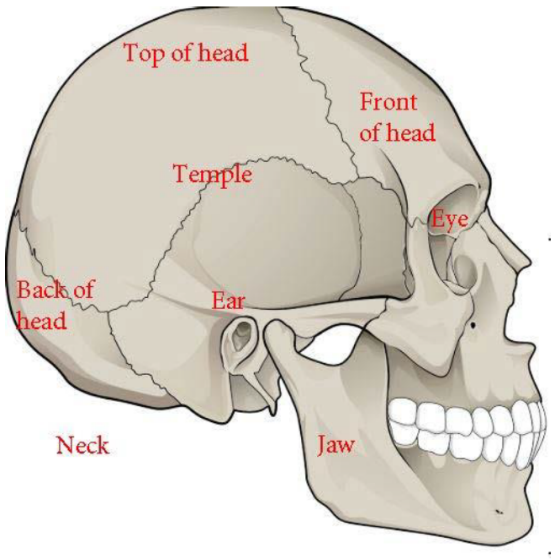
**If YES to above, please focus the following questions on your worst disability headache type*

6. Using the image below as a guide, please check where your headaches are generally located (*circle left and/or right when indicated*)

◯ Temple (R L) ◯ Back of head ◯ Front of head ◯ Ear (R L)

◯ Top of head (R L) ◯ Eye (R L) ◯ Neck ◯ Jaw

◯ Around head ◯ Other _____



7. Your headaches are worse in the:				
◯ morning	◯ afternoon	◯ evening	◯ during the night	◯ no pattern
8. Are your headaches worse lying down or standing?		◯ Lying down	◯ Standing	
9. Do your headaches wake you up in the middle of the night?		◯ Yes	◯ No	If yes, how often:_____?

10. Do you have other symptoms during your headache?
**mark all that apply*

◯ nausea or upset stomach/ vomiting	◯ sensitivity to smells	◯ Sensitivity to light (prefer a dark room)
◯ Difficulty thinking/concentrating/focus	◯ Sensitivity to sound (prefer a quiet room)	◯ Difficulty speaking/slurred speech
◯ Sore/stiff neck	◯ Increased urination	◯ Vision changes (blurred, spots, patterns)
◯ Anxiety	◯ Eye tearing in only ONE EYE	◯ Irritability
◯ Runny nose in only ONE NOSTRIL	◯ Memory problems	◯ Ringing in ears
◯ Increased appetite	◯ Decreased appetite	◯ Eye redness (R L Both)
◯ Drooping eyelid (R L Both)	◯ Diarrhea	◯ Swelling of eyelid (R L Both)
◯ Constipation	◯ Change in pupil (larger smaller)	◯ Insomnia
◯ Dizziness (lightheaded, woozy)	◯ Vertigo (the room appears to spin)	◯ Sleepiness
◯ Numbness/tingling (R L Both)	◯ Confusion	◯ Facial droop, droopy eyelid, unable to move one arm or leg
◯ Imbalance		

11. Do you have any of the following symptoms before your headache begins:
**check all that apply*

◯ Flashing lights	◯ Loss of vision in one eye	◯ Tunnel vision	◯ Spots: bright/dark
◯ Zigzag lines	◯ Loss of vision on one side	◯ Double vision	◯ Geometric forms
◯ Wavy lines	◯ Total blindness	◯ Distorted vision	◯ Numbness/tingling (R L Both)
◯ Speech difficulty	◯ Vertigo	◯ Dizziness/unsteadiness	◯ Light-headedness
◯ One-sided weakness (R L Both)	◯ Confusion / déjà vu / hallucinations	◯ Other: _____	

Appendix 5: Methotrexate SmPC

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metoject 50 mg/ml solution for injection, pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 50 mg methotrexate (as methotrexate disodium).

1 pre-filled syringe of 0.15 ml contains 7.5 mg methotrexate.
1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate.
1 pre-filled syringe of 0.25 ml contains 12.5 mg methotrexate.
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.35 ml contains 17.5 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.
1 pre-filled syringe of 0.45 ml contains 22.5 mg methotrexate.
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.
1 pre-filled syringe of 0.55 ml contains 27.5 mg methotrexate.
1 pre-filled syringe of 0.60 ml contains 30 mg methotrexate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, pre-filled syringe.
Clear, yellow-brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metoject is indicated for the treatment of

– active rheumatoid arthritis in adult patients,
– polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,
– severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients,
– mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

4.2 Posology and method of administration

Metoject should only be prescribed by physicians who are familiar with the various characteristics of the medicinal product and its mode of action. The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the subcutaneous administration to the patient her/himself. In these cases, detailed administration instructions from the physician are obligate. Metoject is injected **once weekly**.
The patient is to be explicitly informed about the fact of administration **once weekly**. It is advisable to determine a fixed, appropriate weekday as day of injection.
Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions).
Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration (see section 5.2 and 4.4).

Dosage in adult patients with rheumatoid arthritis
The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered either

subcutaneously, intramuscularly or intravenously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded. However, doses exceeding 20 mg/week are associated with significant increase in toxicity, especially bone marrow suppression**.** Response to treatment can be expected after approximately 4 – 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10 – 15 mg/m² body surface area (BSA)/**once weekly**. In therapy-refractory cases the weekly dosage may be increased up to 20 mg/m² body surface area/**once weekly**. However, an increased monitoring frequency is indicated if the dose is increased.
Due to limited data availability about intravenous use in children and adolescents, parenteral administration is limited to subcutaneous and intramuscular injection.
Patients with JIA should always be referred to a rheumatology specialist in the treatment of children/adolescents.

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population (see section 4.4).

Dosage in patients with psoriasis vulgaris and psoriatic arthritis
It is recommended that a test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered either subcutaneously, intramuscularly or intravenously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 – 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in patients with Crohn's disease
- Induction treatment:
  25 mg/week administered either subcutaneously, intravenously or intramuscularly.
  Response to treatment can be expected after approximately 8 to 12 weeks.
- Maintenance treatment:
  15 mg/week administered either subcutaneously, intravenously or intramuscularly.

There is not sufficient experience in the paediatric population to recommend Metoject for the treatment of Crohn's disease in this population.

Maximum weekly dose

The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

Patients with renal impairment
Metoject should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)	Dose
≥ 60	100 %
30 – 59	50 %
< 30	Metoject must not be used

See section 4.3.

Patients with hepatic impairment

Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5 mg/dl (85.5 µmol/l), methotrexate is contraindicated.

For the full list of contraindications, see section 4.3.

Use in elderly patients
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Use in patient with a third distribution space (pleural effusions, ascitis)
As the half-life of methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required (see section 5.2 and 4.4).

Method of administration
The medicinal product is for single use only.
Metoject can be given by intramuscular, intravenous or subcutaneous route (in children and adolescents only subcutaneous or intramuscular).

The overall duration of the treatment is decided by the physician.

Note:
If changing the oral application to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Folic acid supplementation may be considered according to current treatment guidelines.

4.3 Contraindications

Metoject is contraindicated in the case of

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- severe liver impairment (see section 4.2),
- alcohol abuse,
- severe renal impairment (creatinine clearance less than 30 ml/min., see section 4.2 and section 4.4),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
- ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy and breast-feeding (see section 4.6),
- concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients must be clearly informed that the therapy has to be administered **once a week**, not every day. Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore, methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

Recommended examinations and safety measures

Before beginning or reinstituting methotrexate therapy after a rest period
Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (at least once a month during the first six months and every three months thereafter)

An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes
2. Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe doses. Any profound drop in whitecell or platelet counts indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.
3. Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications.
   For psoriasis patients the need of a liver biopsy prior to and during therapy is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.
   Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 – 20 %. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

   Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide).
   The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).
4. Renal function should be monitored by renal function tests and urinalysis (see sections 4.2 and 4.3).
   As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal impairment, which may result in severe undesirable effects. Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular when medicinal products are administered concomitantly that affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or that can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.
5. Assessment of respiratory system: Alertness for symptoms of lung function impairment and, if necessary lung function test. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate. Pulmonary symptoms (especially a dry, non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported.
   Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnoea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be

excluded. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate therapy. This lesion can occur at all doses.
In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination results and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Vaccination using live vaccines must not be carried out under methotrexate therapy.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

Radiation-induced dermatitis and sunburn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 5.2).

Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

For the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

Encephalopathy/leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications.

Fertility and reproduction

Fertility
Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration – effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (see section 4.6). The absence of pregnancy must be confirmed before Metoject is used. If women of a sexually mature age are treated, effective contraception must be performed during treatment and for at least six months after.
For contraception advice for men see section 4.6.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

Paediatric population
Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Nitrous oxide
The use of nitrous oxide potentiates the effect of methotrexate on folate, yielding increased toxicity such as severe unpredictable myelosuppression and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use should be avoided.

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products
The probability of methotrexate exhibiting a hepatotoxic effect is increased by regular alcohol consumption and when other hepatotoxic medicinal products are taken at the same time (see section 4.4).
Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine). The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Combined treatment with methotrexate and retinoids like acitretin or etretinate increases the risk of hepatotoxicity.

Oral antibiotics
Oral antibiotics like tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation, by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Antibiotics
Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

Medicinal products with high plasma protein binding
Methotrexate is plasma protein bound and may be displaced by other protein bound medicinal products such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the acidic anti-inflammatory agents, which can lead to increased toxicity when used concurrently.

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents
Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate and higher serum concentrations may be assumed inducing higher haematological toxicity. There is also a possibility of increased toxicity when low dose methotrexate and nonsteroidal anti-inflammatory medicinal products or salicylates are combined.

Medicinal products with adverse reactions on the bone marrow
In the case of medication with medicinal products which may have adverse reactions on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine); attention should be paid to the possibility of pronounced impairment of blood formation.

Medicinal products which cause folate deficiency
The concomitant administration of products which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular care is therefore advisable in the presence of existing folic acid deficiency.

Products containing folic acid or folinic acid
Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

Other antirheumatic medicinal products

An increase in the toxic effects of methotrexate is, in general, not to be expected when Metoject is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprin, cyclosporin).

Sulfasalazine
Although the combination of methotrexate and sulfasalazine can cause an increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulfasalazine, such undesirable effects have only been observed in rare individual cases in the course of several studies.

Mercaptopurine
Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Proton-pump inhibitors
A concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Theophylline
Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Caffeine- or theophylline-containing beverages
An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, black tea) should be avoided during methotrexate therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure. As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.
In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to

cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).
Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.
• Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
• Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in disease-matched patients treated with drugs other than methotrexate.
Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.
When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

Breast-feeding
Methotrexate is excreted in human milk. Because of the potential for serious adverse reactions in breastfed infants, Metoject is contraindicated during breast-feeding (see section 4.3). Therefore breast-feeding must be discontinued prior to and throughout administration.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

4.7 Effects on ability to drive and use machines

Central nervous symptoms such as tiredness and dizziness can occur during treatment, Metoject has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome.

Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite and abnormal liver function tests e.g. increased ALAT, ASAT, bilirubin, alkaline phosphatase. Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

Tabulated list of adverse reactions

The most relevant undesirable effects are suppression of the haematopoietic system and gastrointestinal disorders.

The following headings are used to organise the undesirable effects in order of frequency:

Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data)

Infections and infestations
Uncommon: Pharyngitis.
Rare: Infection (incl. reactivation of inactive chronic infection), sepsis, conjunctivitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare: Lymphoma (see “description” below).

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombopenia.
Uncommon: Pancytopenia.
Very rare: Agranulocytosis, severe courses of bone marrow depression, lymphoproliferative disorders (see "description" below).
Not known: Eosinophilia.

Immune system disorders
Rare: Allergic reactions, anaphylactic shock, hypogammaglobulinaemia.

Metabolism and nutrition disorders
Uncommon: Precipitation of diabetes mellitus.

Psychiatric disorders
Uncommon: Depression, confusion.
Rare: Mood alterations.

Nervous system disorders
Common: Headache, tiredness, drowsiness.
Uncommon: Dizziness.
Very rare: Pain, muscular asthenia or paraesthesia in the extremities, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis.
Not known: Encephalopathy/leukoencephalopathy.

Eye disorders
Rare: Visual disturbances.
Very rare: Impaired vision, retinopathy.

Cardiac disorders
Rare: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders
Rare: Hypotension, thromboembolic events.

Respiratory, thoracic and mediastinal disorders
Common: Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever.
Rare: Pulmonary fibrosis, *Pneumocystis carinii* pneumonia, shortness of breath and bronchial asthma, pleural effusion.
Not known: Epistaxis, pulmonary alveolar haemorrhage.

Gastrointestinal disorders
Very common: Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain.
Common: Oral ulcers, diarrhoea.
Uncommon: Gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis.
Rare: Gingivitis.
Very rare: Haematemesis, haematorrhea, toxic megacolon.

Hepatobiliary disorders (see section 4.4)
Very common: Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).
Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin.
Rare: Acute hepatitis.
Very rare: Hepatic failure.

Skin and subcutaneous tissue disorders
Common: Exanthema, erythema, pruritus.
Uncommon: Photosensitisation, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.

Rare: Increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis.
Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia.

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia, osteoporosis.
Rare: Stress fracture.
Not known: Osteonecrosis of jaw (secondary to lymphoproliferative disorders).

Renal and urinary disorders
Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.
Rare: Renal failure, oliguria, anuria, electrolyte disturbances.
Not known: Proteinuria.

Reproductive system and breast disorders
Uncommon: Inflammation and ulceration of the vagina.
Very rare: Loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge.

General disorders and administration site conditions
Rare: Fever, wound-healing impairment.
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.
Not known: Asthenia.

Description of selected adverse reactions
The appearance and degree of severity of undesirable effects depends on the dose level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is indispensable that patients are monitored regularly by the doctor at short intervals.

Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.

When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur commonly. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via (see details below).

[To be completed nationally]

4.9 Overdose

a) Symptoms of overdose

Toxicity of methotrexate mainly affects the haematopoietic system.

b) Treatment measures in the case of overdose

Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l.

In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA01
Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases and polyarthritic forms of juvenile idiopathic arthritis. Immunomodulating and anti-inflammatory agent for the treatment of Crohn's disease.

Mechanism of action

Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis, chronic polyarthritis and Crohn's disease, is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

International clinical guidelines reflect the use of methotrexate as a second choice for Crohn's disease patients that are intolerant or have failed to respond to first-line immunomodulating agents as azathioprine (AZA) or 6-mercaptopurine (6-MP).

The adverse events observed in the studies performed with methotrexate for Crohn's disease at cumulative doses have not shown a different safety profile of methotrexate than the profile it is already known. Therefore, similar cautions must be taken with the use of methotrexate for the treatment of Crohn's disease as in other rheumatic and non-rheumatic indications of methotrexate (see sections 4.4 and 4.6).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (dosages between 7.5 mg/m² and 80 mg/m² body surface area), the mean bioavailability is approx. 70 %, but considerable interindividual and intraindividual deviations are possible (25 – 100 %). Maximum serum concentrations are achieved after 1 – 2 hours.

Bioavailability of subcutaneous, intravenous and intramuscular injection is comparable and nearly 100%.

Distribution

Approximately 50 % of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations in the form of polyglutamates are found in the liver, kidneys and spleen in particular, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the cerebrospinal fluid in minimal amounts. The terminal half-life is on average 6 – 7 hours and demonstrates considerable variation (3 – 17 hours). The half-life can be prolonged to 4 times the normal length in patients who possess a third distribution space (pleural effusion, ascites).

Biotransformation

Approx. 10 % of the administered methotrexate dose is metabolised intrahepatically. The principle metabolite is 7-hydroxymethotrexate.

Elimination

Excretion takes places, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus.
Approx. 5 – 20 % methotrexate and 1 – 5 % 7-hydroxymethotrexate are eliminated biliary. There is pronounced enterohepatic circulation.

In the case of renal impairment, elimination is delayed significantly. Impaired elimination with regard to hepatic impairment is not known.

5.3 Preclinical safety data

Animal studies show that methotrexate impairs fertility, is embryo- and foetotoxic and teratogenic. Methotrexate is mutagenic *in vivo* and *in vitro*. As conventional carcinogenicity studies have not been performed and data from chronic toxicity studies in rodents are inconsistent, methotrexate is considered **not classifiable** as to its carcinogenicity to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Store below 25 °C. Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Nature of container
Pre-filled syringes of colourless glass (type I) of 1 ml capacity with embedded injection needle. Plunger stoppers of chlorobutyl rubber (type I) and polystyrene rods inserted on the stopper to form the syringe plunger

or

Pre-filled syringes of colourless glass (type I) of 1 ml capacity with embedded injection needle. Plunger stoppers of chlorobutyl rubber (type I), polystyrene rods inserted on the stopper to form the syringe plunger and a safety system to prevent needle stick injury and reuse of the needle.

or
Pre-filled syringes of colourless glass (type I) of 1 ml capacity with enclosed injection needle. Plunger stoppers of chlorobutyl rubber (type I) and polystyrene rods inserted on the stopper to form the syringe plunger.

Pack sizes
Pre-filled syringes containing 0.15 ml, 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml, 0.50 ml, 0.55 ml or 0.60 ml solution are available in packs of 1, 4, 5, 6, 10, 11, 12 and 24 syringes with embedded s.c. injection needle and alcohol pads.

and

Pre-filled syringes containing 0.15 ml, 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml, 0.50 ml, 0.55 ml or 0.60 ml solution are available in packs of 1, 4, 5, 6, 10, 11, 12 and 24 syringes with embedded s.c. injection needle with safety system and alcohol pads.

and

Pre-filled syringes containing 0.15 ml, 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml, 0.50 ml, 0.55 ml or 0.60 ml solution are available in packs of 1, 4, 5, 6, 10, 11, 12 and 24 syringes with enclosed s.c. injection needle and alcohol pads.

For i.m and i.v use, a needle suitable for these routes of administration must be used: The needle enclosed in the pack is suitable for s.c. use only.

All pack sizes are available with graduation marks.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The manner of handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metoject.

Methotrexate should not come into contact with the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with ample amount of water.

For single use only.

Any unused medicinal product or waste should be disposed of in accordance with local requirements.

In some regions Metoject may be marketed with a safety system to prevent needle stick injury and reuse of the needle.

Instructions for subcutaneous use of Metoject <u>without</u> safety system
The best places for the injection are:
- upper thighs,
- abdomen except around the navel.

1. Clean the area around the chosen injection site (e.g. by using the enclosed alcohol pad).
2. Pull the protective plastic cap straight off.
3. Build a skin fold by gently squeezing the area at the injection site.
4. The fold must be held pinched until the syringe is removed from the skin after the injection.
5. Push the needle fully into the skin at a 90-degree angle.
6. Push the plunger down slowly and inject the liquid underneath the skin. Remove the syringe from the skin at the same 90-degree angle.

Instructions for subcutaneous use of Metoject <u>with</u> safety system
The best places for the injection are:
- upper thighs,
- abdomen except around the navel.

1. Clean the area around the chosen injection site (e.g. by using the enclosed alcohol pad).
2. Pull the protective plastic cap straight off.
3. Build a skin fold by gently squeezing the area at the injection site.
4. The fold must be held pinched until the syringe is removed from the skin after the injection.
5. Push the needle fully into the skin at a 90-degree angle.
6. Push the plunger down slowly and inject the liquid underneath the skin. Remove the syringe from the skin at the same 90-degree angle.
7. A protective cover will automatically enclose the needle.

Note: The protection system that is triggered by the release of the protective cover can only be activated when the syringe has been emptied completely by pushing down the plunger as far as it goes.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH

Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER

<[To be completed nationally]>

9. DATE OF FIRST MARKETING AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 October 2008
Date of latest renewal: 02 October 2013

10. DATE OF REVISION OF THE TEXT

2018-10-05