CLINICAL STUDY PROTOCOL

Project Number:	GLPG3970
Study Number:	GLPG3970-CL-209
Study Title:	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy and pharmacokinetics of GLPG3970, administered orally for 6 weeks in adult subjects with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate
Short Study Title:	A study evaluating the effects of GLPG3970 given as an oral treatment for 6 weeks in adults with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate
Clinical Study Phase:	2
Protocol Version:	1.0
Date:	29-May-2020
Status:	Final
EudraCT No:	2020-000658-83 CT.gov No: to be confirmed
IND No:	not applicable
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium
Clinical Scientist:	[redacted]
Translational Medicine Leader:	[redacted]

General Protocol

Confidentiality Statement

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE)**, a special situation (see Section 11.1.6) or in case of **pregnancy** during the clinical study the investigator must report this immediately, and under no circumstances later than 24 hours following the knowledge of the event as follows:

E-mail: [redacted]

or

SGS Medical Affairs SAE Fax [redacted]

In case of medical questions during the course of the study, the investigator must contact the contact research organization (CRO) medical monitor or if unavailable, his/her back-up, the sponsor scientific leader for all scientific, protocol and investigational product (IP) related questions and the sponsor translational medicine leader for all safety related questions:

CRO medical monitor:

[redacted] Medical Emergency Contact Center

Phone: [redacted]
[redacted])
[redacted] (alternative number)

Sponsor scientific leader:

[redacted]

Sponsor contact number:

[redacted]

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CLINICAL STUDY PROTOCOL HISTORY

Clinical Study Protocol (CSP) / Amendment #	**Date**	**Main Rationale** **General / Country-Specific**
CSP Version 1.0	29-May-2020	Initial CSP Version General

SUMMARY OF CHANGES

Not applicable because this is the initial clinical study protocol (CSP).

LIST OF TABLES

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LIST OF APPENDICES

[redacted]

[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

[redacted]	[redacted]
ACR	American College of Rheumatology
ADL	Activities of Daily Living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
bDMARD	biologic disease-modifying anti-rheumatic drug
bpm	beats per minute
BMI	body mass index
[redacted]	[redacted]
CI	confidence interval
CIA	collagen-induced arthritis
CL	clearance
CLCr	creatinine clearance
CL/F	apparent total clearance
C_{max}	maximum observed plasma concentration
CRF	case report form
CRP	C-reactive protein
CRO	contract research organization

CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CTx	serum C terminal telopeptide type I collagen
CYP	cytochrome P450
DAS28	disease activity score based on 28 joints
DBP	diastolic blood pressure
DMARD	disease-modifying anti-rheumatic drug
DTP	direct to patient
ECG	electrocardiogram
ED	early discontinuation
EU	European Union
EULAR	European League Against Rheumatism
F	bioavailability
FIH	first-in-human
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
[redacted]	[redacted]
HbA1c	hemoglobin A1c
HBsAg	hepatitis B virus surface antigen

HDL	high-density lipoprotein
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HOMA-IR	Homeostatic model assessment of insulin resistance
hsCRP	high sensitivity C-reactive protein
IB	investigator's brochure
IC_{50}	half maximum inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL	interleukin
IP	investigational product
INR	international normalized ratio
IRB	Institutional Review Board
IXRS	interactive voice/web response system
JAK	Janus kinase
LDL	low-density lipoprotein
LFT	liver function test
LPS	lipopolysaccharide
LRV	lower reference value
MMRM	mixed models for repeated measures
mRNA	messenger ribonucleic acid
MTX	methotrexate

NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
P1NP	serum N terminal propeptide type I collagen
PBMC	peripheral blood mononuclear cells
[redacted]	[redacted]
PK	pharmacokinetic
pop-PK	population pharmacokinetics
q.d.	once daily
QTcF	QT interval corrected for the heart rate using Fridericia's formula
QTv	QT interval corrected by heart rate using the van de Water formula
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
[redacted]	[redacted]
SIK	salt-inducible kinase
SJC66	swollen joint count evaluated in 66 joints
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC68	tender joint count evaluated in 68 joints

TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TV	target value
ULN	upper limit of normal
VAS	visual analog scale
Vss	volume of distribution at steady state
WOCBP	women of childbearing potential

Definition of Terms

BMI	body mass index Weight (kg) / (height [m])^2
QTcF	QT interval corrected for heart rate using Fridericia's formula: $QTcF = QT/RR^{1/3}$ RR = the interval from the onset of one QRS complex to the onset of the next QRS complex
DAS28 (CRP)	disease activity score based on 28 joints DAS28 (CRP) = 0.56 x $\sqrt{TJC28}$ + 0.28 x $\sqrt{SJC28}$ + 0.36 x Ln[1+CRP(in mg/L)] + 0.014 x patient's disease activity visual analog scale (VAS, in mm) + 0.96 (Mack, Hsia, & Aletaha, 2017) TJC28 and SJC28 are the 28 joint counts for tenderness and swelling. Ln = natural logarithm.
[redacted]	[redacted]

[redacted]

HOMA-IR Homeostatic model assessment of insulin resistance

HOMA-IR= (fasting insulin [mU/mL] x fasting glucose [mg/dL])/405

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

1. CLINICAL STUDY PROTOCOL SYNOPSIS

Title of Study

A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy and pharmacokinetics of GLPG3970, administered orally for 6 weeks in adult subjects with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate

Short Title of Study

A study evaluating the effects of GLPG3970 given as an oral treatment for 6 weeks in adults with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate

Phase of Development: Phase 2

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of GLPG3970 compared to placebo on the signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA and an inadequate response to methotrexate (MTX).	Change from baseline in DAS28 (C-reactive protein [CRP]) at Week 6.
Secondary	
To evaluate the safety and tolerability of GLPG3970 compared to placebo in subjects with moderately to severely active RA and an inadequate response to MTX.	Number, incidence and severity of treatment-emergent adverse events (TEAEs).
To characterize the pharmacokinetics (PK) of GLPG3970 in subjects with moderately to severely active RA and an inadequate response to MTX.	Observed GLPG3970 plasma trough concentrations (C_{trough}).

[redacted]

[redacted]

The study is planned to randomize 25 subjects in a 3:2 ratio (15 subjects planned to receive GLPG3970 and 10 subjects planned to receive placebo).

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter parallel-group study evaluating GLPG3970 in adult subjects with moderately to severely active RA and an inadequate response to MTX. In this study, subjects will receive 1 dose level of GLPG3970 (400 mg once daily [q.d.]) or placebo on top of their stable dose and dosing regimen of MTX.

The study will consist of 3 study periods:

- Screening period: up to 3 weeks with 1 study visit.
- Double-blind treatment period: 6 weeks with 4 study site visits (Days 1, 15, 29, and 43) and 1 telephone call (Day 8).
- Follow-up (FU) period: 2 weeks with 1 study visit.

A schematic diagram of clinical study design, procedures, and stages is provided below.

Study Duration

Subjects will participate in the study for a maximum of 11 weeks (screening to FU) and will receive oral GLPG3970 or placebo, as a reconstituted oral solution, q.d. for 6 weeks.

Main Criteria for Inclusion and Exclusion

Main Inclusion Criteria

1. Male or female subject ≥18 and <65 years of age, on the date of signing the informed consent form (ICF).
2. A body mass index (BMI) between 18–32 kg/m^2, inclusive.
3. Diagnosis of RA ≥6 months prior to screening AND meeting the 2010 ACR/ EULAR criteria of RA AND ACR functional class I-III.
4. Have ≥6 swollen joints (from a SJC66) AND ≥8 tender joints (from a TJC68) at screening and at the baseline visit (Visit 1) prior to the first IP dosing.
5. DAS28 (CRP) >3.2 (moderate disease) at screening.
6. Screening serum high sensitivity CRP (hsCRP) > upper limit of normal (ULN, central laboratory reference: ≤ 5.0 mg/L).
7. Inadequate response to MTX, i.e. treatment-experienced subjects who demonstrated inadequate clinical response during treatment with MTX.
8. Have received MTX for ≥6 months and on stable dose (10 to 20 mg/week) of MTX for at least 4 weeks prior to screening and willing to continue on their current stable dose and dosing regimen for the duration of the study.
9. If taking systemic steroids, prednisone equivalent at a dose of ≤10 mg/day and stable for at least 4 weeks prior to the first IP dosing.

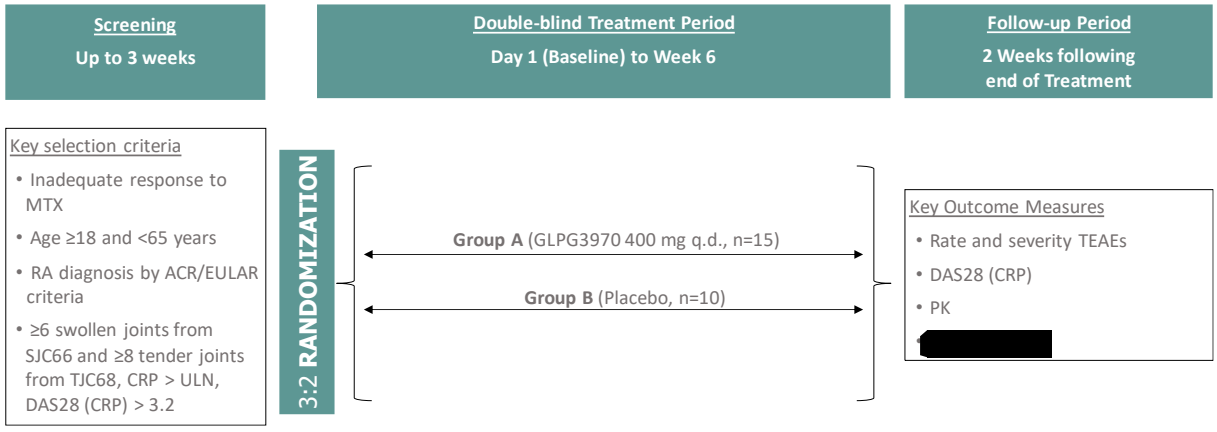
Main Exclusion Criteria

1. Current therapy with any conventional disease-modifying anti-rheumatic drug (DMARD) other than MTX, including
   a. oral or injectable gold, sulfasalazine, antimalarials, azathioprine, or D-penicillamine within 4 weeks prior to screening,
   b. cyclosporine within 8 weeks prior to screening, and
   c. leflunomide within 3 months prior to screening or a minimum 4 weeks prior to screening if after 11 days of standard cholestyramine therapy.
2. Current or previous treatment with a biologic DMARD (bDMARD). Except for subjects who received bDMARDs only in a single clinical study setting:
   a. For whom the last dose of bDMARD ≥6 months prior to screening (12 months for rituximab or other lymphocyte depleting agents), AND;
   b. For whom the bDMARD was effective, without being discontinued due to lack of efficacy.
3. Subjects who received an intra-articular or parenteral corticosteroid injection within 4 weeks prior to screening.
4. Subjects who received a prior surgical intervention within 12 weeks prior to screening or likely requirement for surgery during the study.
5. Subject has a history of tuberculosis (TB) diagnosis or evidence of active or latent infection with *Mycobacterium tuberculosis* as defined by one of the following assessments:
   a. Positive QuantiFERON-TB Gold test result at screening, OR

b. Chest radiograph (posterior anterior view) taken within 12 weeks prior to screening, read by a qualified radiologist or pulmonologist, with evidence of current active TB or old inactive TB.

6. Subject has any active systemic infection within the last 2 weeks prior to first IP dosing, or poorly controlled chronic cardiac, pulmonary, or renal disease.
7. Subject has a known or suspected history of or a current immunosuppressive condition, or a history of invasive opportunistic infections (e.g. human immunodeficiency virus [HIV] infection, histoplasmosis, listeriosis, coccidiodmycosis, pneumocystosis, aspergillosis).
8. Subject has a chronic hepatitis B virus (HBV) infection, as defined by persistent HBV surface antigen (HBsAg) positivity. Subject has hepatitis C virus (HCV) infection, as defined by positive HCV antibody at screening and detectable HCV viremia. Subjects with positive HCV antibody must undergo reflex HCV RNA testing, and subjects with HCV RNA positivity will be excluded. Subjects with positive HCV antibody and negative HCV RNA are eligible.
9. Subject testing positive at screening for SARS-CoV-2 infection as detected by real time polymerase chain reaction (RT-PCR), subjects presenting any signs or symptoms as detected at baseline following careful physical examination (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, others) or reporting any signs and symptoms for the 2 preceding weeks, or subjects who have been exposed to individuals with confirmed or suspected diagnosis of SARS-CoV-2 within 2 weeks prior to baseline. In addition, any other locally applicable standard diagnostic criteria may also apply to rule out SARS-CoV-2 infection.

Treatment and Treatment Schedule



Investigational Medicinal Product, Dosage, and Mode of Administration

GLPG3970 will be provided as a powder and solvent for oral solution, to be reconstituted prior to use. The final dosage form for administration is an oral solution containing 400 mg of the active pharmaceutical ingredient G1567970 (G1567970 is the compound code for

GLPG3970). A placebo powder and solvent for oral solution, to be reconstituted prior to use, will also be provided.

Statistical Analysis

Safety Analysis

All safety analyses will be performed using the Safety Analysis Set, consisting of all subjects who used at least 1 dose of IP. All safety data collected on or after the first dose of IP administration up to the last contact after the last dose of IP, unless specified otherwise, will be summarized by treatment group according to the IP received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead electrocardiograms (ECGs).

Efficacy Analysis

All efficacy analyses will be performed using the Full Analysis Set, consisting of all randomized subjects who received/used at least 1 dose of IP. Continuous efficacy endpoints, including the primary endpoint: mixed model for repeated measures to compare treatment groups, with a 90% confidence interval (CI) of the treatment difference at each time point. Binary efficacy endpoints will be presented with a 90% exact CI of the treatment difference at each time point. For the primary efficacy endpoint: go/consider/stop methodology will be used additionally to provide further insight in the treatment effect.

PK Analysis

Descriptive statistics will be done on C_{trough} plasma levels for GLPG3970. Observed plasma C_{trough} for GLPG3970 [redacted] will be reported in the clinical study report (CSR).

Observed GLPG3970 plasma concentrations will be analyzed using a population PK approach to characterize the PK profile of GLPG3970. This analysis will provide simulated population pharmacokinetic (pop-PK) parameters for GLPG3970, [redacted]

2. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory and joint degenerative disease that affects almost 1% of the adult population worldwide. The onset of RA classically occurs around 40 years of age (Oton & Carmona, 2020) and RA has a higher prevalence in women. The disease is characterized by pain, stiffness, and restricted mobility due to a persistent symmetrical inflammation of the synovial membrane of multiple joints that ultimately results in irreversible damage of the joint cartilage and bone (Smolen, Aletaha, Koeller, Weisman, & Emery, 2007). The treatment of RA aims to reduce synovial inflammation, relieve pain, prevent joint damage and deterioration of physical function and the final goal is to achieve remission or at least low disease activity for all patients. To date, monotherapy with methotrexate (MTX), a disease-modifying anti-rheumatoid drug (DMARD), is the recommended first-line treatment for patients with RA. Many patients fail to respond or don't achieve disease remission with MTX (Chatzidionysiou & Sfikakis, 2019; Köhler, Günther, & Kaudewitz, 2019). In clinical trials, remission rates with MTX (with or without corticosteroids) range from 15% to 50.8% in subjects with early RA (disease duration <1 year) and from 7.6% to 28% in subjects with RA disease duration >1 year (Chatzidionysiou & Sfikakis, 2019). For patients with moderate or high disease activity despite DMARD therapy, it is recommended to use a combination of DMARDs with a tumor necrosis factor inhibitor (TNFi), or a non-TNF biologic and, in the case of established RA, a Janus kinase (JAK) inhibitor can be used (Smolen, et al., 2020). Glucocorticoids are often used in combination during acute disease flares to relieve pain and swelling fast and to gain control of the inflammation. A number of pro-inflammatory cytokines including TNF and interleukin-6 (IL-6) are involved in the pathophysiology of RA and thus, biologic DMARDs (bDMARDs), targeting those cytokines and cells of the immune system have been approved for the treatment of RA (such as adalimumab, etanercept, infliximab, abatacept, rituximab, tocilizumab etc.). Due to the inconvenience of parenteral administration, safety, and tolerability issues (e.g. increased risk for infection and potential immunogenicity), and failure or only partial response to biologicals, there is still a need for safer, better tolerable, and orally active drugs with a different mechanism of action that can effectively modify the disease course. Oral, small-molecule inhibitors of intracellular kinases might bring therapeutic benefit in a wide range of inflammatory diseases and could address this need. More recently, JAK inhibitors demonstrated good efficacy in patients with RA. Even though many efficient drugs are currently available for the treatment for RA, many patients still suffer from ongoing symptoms and don't achieve the final goal which is sustained disease remission and drug-free remission (Ajeqanova & Huizinga, 2017). Thus, there is still unmet medical need for patients with RA.

GLPG3970 has a dual mechanism of action with the potential to improve upon the currently available treatments, via the induction of immunoregulatory mechanisms in addition to its anti-inflammatory properties. GLPG3970 is an oral, selective, small-molecule serine/threonine salt-inducible kinase (SIK) 2 and 3 inhibitor. These kinases provide a molecular switch in the control of pro- and anti-inflammatory cytokine production. Inhibition of these targets blocks the production of pro-inflammatory cytokines (TNFα, IL-12) and increases IL-10 levels, which has a tolerogenic effect, by activated macrophages and dendritic cells, thereby, converting the inflammatory state of these cells toward regulatory and tolerogenic phenotypes. In a mouse model of RA, treatment with GLPG3970 reduced disease activity.

For more details refer to the latest version of the investigator's brochure (IB) and its relevant updates/addenda.

This clinical study will be conducted in compliance with this clinical study protocol (CSP), the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) Guideline E6, and applicable local ethical and legal requirements (see also Section 12).

2.1. Background - Nonclinical Studies

2.1.1. Nonclinical Pharmacokinetics

[redacted]

2.1.2. Safety Pharmacology

[redacted]

2.1.3. General Toxicology

[redacted]

[redacted]

[redacted]

2.1.4. Genotoxicity

[redacted]

2.1.5. Embryo-fetal Development Toxicity

The safety of GLPG3970 for use during pregnancy has not been established. [redacted]

[redacted]

2.1.6. Phototoxicity

[redacted]

2.2. Background - Clinical Studies

[redacted]

[redacted]

[redacted]

3. CLINICAL STUDY OBJECTIVES

3.1. Primary Objectives

- To evaluate the effect of GLPG3970 compared to placebo on the signs and symptoms of RA in subjects with moderately to severely active RA and an inadequate response to methotrexate (MTX).

3.2. Secondary Objective

- To evaluate the safety and tolerability of GLPG3970 compared to placebo in subjects with moderately to severely active RA and an inadequate response to MTX.
- To characterize the PK of GLPG3970 in subjects with moderately to severely active RA and an inadequate response to MTX.

[redacted]

4. ENDPOINTS

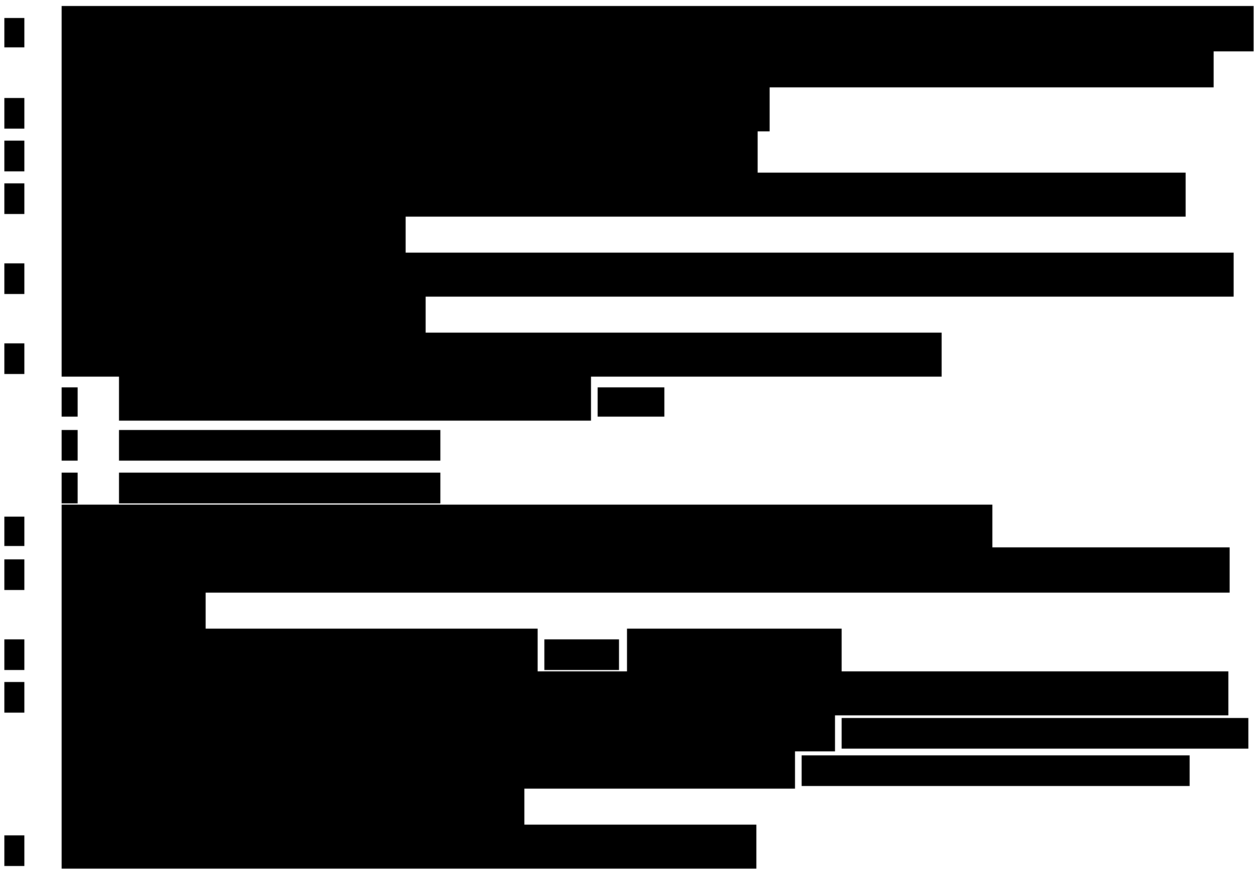
4.1. Primary Endpoints

- Change from baseline in DAS28 (C-reactive protein [CRP]) at Week 6.

4.2. Secondary Endpoints

- Number, incidence and severity of treatment-emergent adverse events (TEAEs).
- Observed GLPG3970 plasma trough concentrations (C_{trough}).

4.3. Other Endpoints



5. INVESTIGATIONAL PLAN

5.1. Clinical Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter parallel-group study evaluating GLPG3970 in adult subjects with moderately to severely active RA and an inadequate response to MTX. In this study, subjects will receive 1 dose level of GLPG3970 (400 mg once daily [q.d.]) or placebo on top of their stable dose and dosing regimen of MTX.

The study is planned to randomize 25 subjects in a 3:2 ratio (15 subjects planned to receive GLPG3970 and 10 subjects planned to receive placebo).

The study will consist of 3 study periods:

- Screening period: up to 3 weeks with 1 study visit.
- Double-blind treatment period: 6 weeks with 4 study site visits (Days 1, 15, 29, and 43) and 1 telephone call (Day 8).
- Follow-up (FU) period: 2 weeks with 1 study visit.

Subjects will participate in the study for a maximum of 11 weeks (screening to FU) and will receive oral GLPG3970 or placebo, as a reconstituted oral solution, q.d. for 6 weeks.

Refer to the Schedule of Activities (Section 8.11) for further details.

A schematic diagram of clinical study design, procedures and stages is provided in Figure 1.

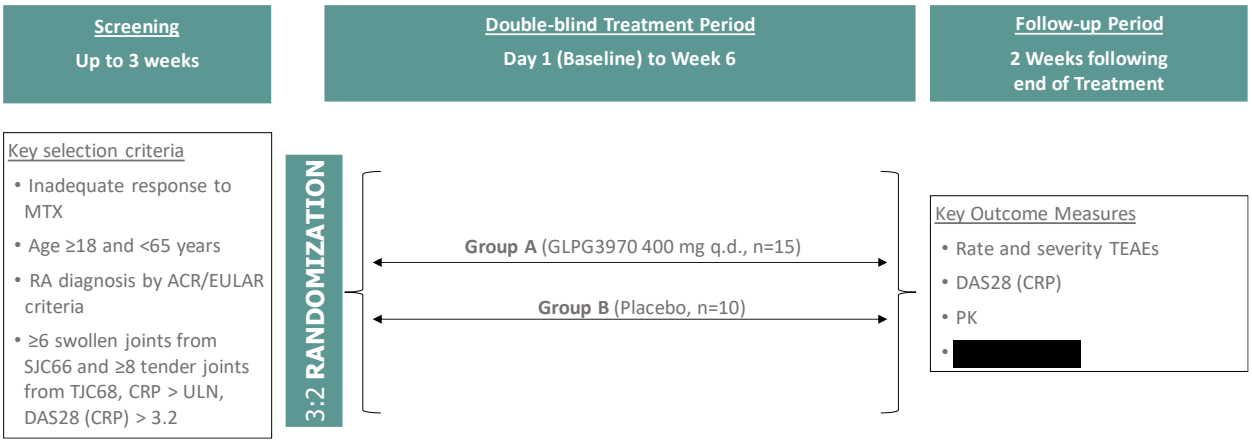


Figure 1 Schematic Diagram

For detailed information regarding dosage form, packaging and labeling of the investigational product (IP) refer to Section 7.2, "Dosage and Administration" and Section 7.3, "Packaging, Labeling and Distribution".

5.2. Start and End of Study Definition

The study start is defined when the first informed consent form (ICF) is signed. The end of the study is reached when the last FU visit, as planned according to the Schedule of Activities (Section 8.11), for the last subject is performed.

5.3. Clinical Study Rationale

Published data showed that RA results from a breakdown of immune tolerance (Smolen, Aletaha, Koeller, Weisman, & Emery, 2007). GLPG3970 displays a unique dual mode of action with an anti-inflammatory component (reduction of pro-inflammatory cytokines by activated monocytes, macrophages, dendritic cells and T cells) coupled with a robust induction of immunoregulatory mechanisms (induced production of IL-10) in activated monocytes, macrophages and dendritic cells. The mouse collagen-induced arthritis (CIA) model is one of the most widely used models for the study of new therapeutic treatment options in RA and mimics the characteristics of human RA. GLPG3970 has demonstrated therapeutic potential in this model at the highest dose of 60 mg/kg b.i.d. tested, similar to anti-TNFα treatment used as active comparator in the model. Treatment with GLPG3970 showed a significant effect on protection against bone erosion (Larsen score) and significantly reduced the production of total immunoglobulin G (IgG) levels, quantified in plasma as a measure of the autoreactive B cell state in the arthritic CIA model. These data provide strong rationale for the evaluation of GLPG3970 in subjects with RA.

The double-blind, placebo-controlled, randomized, parallel-group design is a standard design for a first study of GLPG3970 in subjects with RA.

The use of a placebo arm in this type of design has an important value, as "placebo-response" is known to occur during clinical studies. Although the reported magnitude of this response varies from study to study, it can be substantial. Hence, the addition of a placebo arm enables a control for potential influences derived from the natural course of RA and other effects that are inherent to overall medical care. The use of placebo for 6 weeks in a 3:2 ratio is deemed acceptable by the RA community and justified given the limited treatment duration. Low stable, doses of prednisone and MTX are allowed as background therapy to avoid high placebo-response and side effects due to higher doses of steroids.

MTX is the most commonly prescribed conventional DMARD in RA treatment. Subsequently, subjects with inadequate response to MTX who express signs of active disease at screening are a commonly used subject population for clinical studies evaluating the efficacy of novel RA treatments in comparison with placebo.

During this study, initial signals in potential benefit after 6 weeks treatment will be evaluated including improvements in disease activity. These are endpoints commonly assessed in RA studies. The change from baseline in the DAS28 (CRP) at Week 6 is a semi-continuous clinical score, and the current sample size should be sufficient to allow the detection of an efficacy signal against the selected target value of -1.6 and a lower reference value of -0.6. The selected target value will represent an effect better than current available therapies.

5.4. Dosing Rationale

The dose of 400 mg q.d. GLPG3970 will be used in this study. [redacted]

5.5. Potential Risks and Benefits

GLPG3970 has been studied in a nonclinical setting (Section 2.1) and is being studied in a FIH study (Section 2.2) where the single and multiple ascending dose parts of the study are completed up to the dose of 400 mg q.d. GLPG3970 was well tolerated at all dose levels studied in the FIH study. Study GLPG3970-CL-209 is the first study where GLPG3970 is being administered to subjects with RA.

[redacted]

GLPG3970 has a novel dual mechanism of action, which is intended to restore the balance of the immune system by reducing several mediators of inflammation and by improving immune-regulatory mechanisms that may be impaired in autoimmune diseases such as, for example, RA, psoriasis, and inflammatory bowel disease. Thus, this may weaken the immune response and can potentially increase subject's risk to developing infections (opportunistic infections, SARS-CoV-2, etc). Careful monitoring and reporting of signs and symptoms is therefore required, to enable prompt medical evaluation and pharmacological or clinical intervention.

Based on the mechanism of action of GLPG3970 and its potential to control pro-inflammatory and immunomodulating cytokines, such as TFNα and IL-10, an improvement of clinical symptoms of RA may be derived.

Risk Mitigation

Mitigation measures have been taken to ensure safety of the subjects targeting population selection, dose, concomitant medications, and safety surveillance on certain laboratory parameters and biomarkers. Information on important safety risks is included in the latest version of the IB.

In the forthcoming study subjects' risk will be minimized by implementing conservative eligibility criteria, including RT-PCR testing to exclude subjects with SARS-CoV-2, by standard laboratory tests, by collecting TEAEs throughout the study, and monitoring of subjects for infection symptoms. Any potential negative effects of GLPG3970 will be carefully assessed through regular physical assessments and laboratory monitoring that will happen at every visit. Laboratory alerts will be set up for the study in order to early inform the study investigator and the sponsor on highly abnormal laboratory values (severity Grade 3 and above). A Data Safety Monitoring Committee will monitor unblinded data.

- [redacted]
- The selection of the dose proposed for this study lies within the exposure safety limits, defined based on nonclinical safety studies, and exposures previously shown to be safe and well tolerated in healthy male subjects.
- [redacted]

For more details refer to the latest version of the IB and its relevant updates/addenda.

Subjects at risk of tuberculosis, HIV positive subjects, subjects testing positive for hepatitis B or C and subjects tested positive for SARS-CoV-2 are excluded from the study. Given this study

may be performed during a SARS-CoV-2 pandemic, the age limit of participants was set to 65 years of age and appropriate measures should be taken to minimize the risk of SARS-CoV-2 infection for subjects participating in the study as well as study site personnel. Local guidelines to prevent SARS-CoV-2 infection should be adhered to and a leaflet should be made available for all subjects detailing the SARS-CoV-2 safety measures to be taken.
In case a randomized subject is not available to attend a scheduled study visit on site due to SARS-CoV-2 travel restrictions, a phone call or a televisit may be conducted instead. It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow and the subject agrees, trained study staff or trained personnel are encouraged to collect study assessments at the study subjects' home or a local facility if social distancing and hygiene rules can be applied.
Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visit assessments and the alternative arrangements need to be adequately documented. Direct to patient (DTP) shipments are possible if needed. Subjects presenting with signs and symptoms of infection, including SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and SARS-CoV-2 testing should be performed.

6. CLINICAL STUDY POPULATION

6.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Male or female subject ≥18 and <65 years of age, on the date of signing the ICF.
2. A body mass index (BMI) between 18–32 kg/m^2, inclusive.
3. Diagnosis of RA ≥6 months prior to screening AND meeting the 2010 ACR/EULAR criteria of RA AND ACR functional class I-III.
4. Have ≥6 swollen joints (from a SJC66) AND ≥8 tender joints (from a TJC68) at screening and at the baseline visit (Visit 1) prior to the first IP dosing.
5. DAS28 (CRP) >3.2 (moderate disease) at screening.
6. Screening serum high sensitivity CRP (hsCRP) > upper limit of normal (ULN, central laboratory reference: ≤ 5.0 mg/L).
7. Inadequate response to MTX, i.e. treatment-experienced subjects who demonstrated inadequate clinical response during treatment with MTX.
8. Have received MTX for ≥6 months and on stable dose (10 to 20 mg/week) of MTX for at least 4 weeks prior to screening and willing to continue on their current stable dose and dosing regimen for the duration of the study.
9. If taking systemic steroids, prednisone equivalent at a dose of ≤10 mg/day and stable for at least 4 weeks prior to the first IP dosing.
10. If taking non-steroidal anti-inflammatory drugs (NSAIDs), these must be at a stable dose for at least 2 weeks prior to first IP dosing.
11. Female subjects of childbearing potential must have a negative highly sensitive (serum beta human chorionic gonadotropin) pregnancy test at screening. Female subjects of non-

childbearing potential must have a negative FSH test at screening or must be at least 6 months permanently surgically sterile (bilateral oophorectomy, i.e. surgical removal of ovaries, bilateral salpingectomy or hysterectomy, i.e. surgical removal of uterus).

12. Female subject of child bearing potential or male subject must agree to use highly effective contraception/preventive exposure measures (as described in Section 6.3.1).
13. Able and willing to comply with the CSP requirements (e.g. opening and reconstituting the IP formulation) and must sign and date the ICF as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), prior to any screening evaluations.
14. Able and willing to comply with restrictions on prior and concomitant medication as described in Section 6.3.2.

6.2. Exclusion Criteria

Subjects meeting one or more of the following criteria cannot be enrolled in this clinical study:

1. Current therapy with any conventional DMARD other than MTX, including
   a. Oral or injectable gold, sulfasalazine, antimalarials, azathioprine, or D-penicillamine within 4 weeks prior to screening,
   b. Cyclosporine within 8 weeks prior to screening, and
   c. Leflunomide within 3 months prior to screening or a minimum 4 weeks prior to screening if after 11 days of standard cholestyramine therapy.
2. Current or previous treatment with a bDMARD. Except for subjects who received bDMARDs only in a single clinical study setting:
   a. For whom the last dose of bDMARD ≥6 months prior to screening (12 months for rituximab or other lymphocyte depleting agents), AND;
   b. For whom the bDMARD was effective, without being discontinued due to lack of efficacy.
3. Subjects who received an intra-articular or parenteral corticosteroid injection within 4 weeks prior to screening.
4. Subjects who received a prior surgical intervention within 12 weeks prior to screening or likely requirement for surgery during the study.
5. Subject has a history of tuberculosis (TB) diagnosis or evidence of active or latent infection with *Mycobacterium tuberculosis* as defined by one of the following assessments:
   a. Positive QuantiFERON-TB Gold test result at screening, OR
   b. Chest radiograph (posterior anterior view) taken within 12 weeks prior to screening, read by a qualified radiologist or pulmonologist, with evidence of current active TB or old inactive TB.
6. Subject has any active systemic infection within 2 weeks prior to first IP dosing, or poorly controlled chronic cardiac, pulmonary, or renal disease.
7. Subject has a known or suspected history of or a current immunosuppressive condition, or a history of invasive opportunistic infections (e.g. HIV infection, histoplasmosis, listeriosis, coccidiodmycosis, pneumocystosis, aspergillosis).
8. Subject has a chronic hepatitis B virus (HBV) infection, as defined by persistent HBV surface antigen (HBsAg) positivity. Subject has hepatitis C virus (HCV) infection, as defined

by positive HCV antibody at screening and detectable HCV viremia. Subjects with positive HCV antibody must undergo reflex HCV RNA testing, and subjects with HCV RNA positivity will be excluded. Subjects with positive HCV antibody and negative HCV RNA are eligible.

9. Subject testing positive at screening for SARS-CoV-2 infection as detected by real time polymerase chain reaction (RT-PCR), subjects presenting any signs or symptoms as detected at baseline following careful physical examination (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, others) or reporting any signs and symptoms for the 2 preceding weeks, or subjects who have been exposed to individuals with confirmed or suspected diagnosis of SARS-CoV-2 within 2 weeks prior to baseline (BMJ, 2020) (BMJ, 2020). In addition, any other locally applicable standard diagnostic criteria may also apply to rule out SARS-CoV-2 infection.
10. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.
11. Subject has any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.
12. Subject has a known hypersensitivity to IP ingredients or history of a significant allergic reaction to IP ingredients as determined by the investigator.
13. Subject has any illness, judged by the investigator as relevant for participation in the study, in the 3 months prior to the first dose of the IP.
14. Subject has presence or sequelae of gastrointestinal, liver, kidney (creatinine clearance [ClCr] ≤90 mL/minute, for elderly ≤60 mL/minute, using the Cockcroft-Gault formula: if calculated result is ≤90 mL/minute, for elderly ≤60 mL/minute, if applicable, a 24-hour urine collection can be used) or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
15. Subject has a history of malignancy within the past 5 years prior to screening with the exception of excised and curatively treated non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ cervix which is considered cured with minimal risk of recurrence.
16. Subject concurrently participates or participated in a drug, drug/device or biologic investigational research study within 3 months or 5 half-lives of the IP, whichever is longer, prior to screening.
17. Subject has a history or presence of clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction e.g. known long QT syndrome or a QTcF >450 ms (male), >460 ms (female) detected on the 12-lead ECG. A first-degree atrioventricular block will not be considered as a significant abnormality.
18. Female subject is breast feeding or intending to become pregnant or breastfeed during the study.
19. Subject was vaccinated with a live vaccine within 60 days prior to screening.

6.3. Prohibition and Restrictions

6.3.1. Precautions for Sexual Intercourse

Highly effective contraceptive measures for both males and females of childbearing potential must be documented in the source documents.

6.3.1.1. Female Subjects

Female subjects are considered of non-childbearing potential if they meet one of the following criteria:

- No menses for 12 or more months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanently surgically sterile (bilateral oophorectomy, i.e. surgical removal of ovaries, bilateral salpingectomy or hysterectomy, i.e. surgical removal of uterus).

All other female subjects are considered to be of childbearing potential (WOCBP) and must use one of the following highly effective methods of birth control prior to the first dose of IP, during the clinical study and for at least 35 days after the last dose of IP:

- Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation plus a barrier method.
- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation plus a barrier method.
- Intrauterine device.
- Intrauterine hormone-releasing system plus a barrier method.
- Bilateral tubal occlusion.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only, and lactational amenorrhea method are not acceptable as methods of contraception.

In case a WOCBP has a vasectomized partner, provided that partner is the sole sexual partner of the WOCBP clinical study participant and that the vasectomized partner has received medical assessment of the surgical success, then she is not required to use an additional form of contraception.

Within these limits, the specific forms of contraception employed are left to the discretion of the subject, the investigator, and/or the subject's physician.

The safety of GLPG3970 during breastfeeding is unknown. Nursing women are not allowed to take part in this clinical study.

6.3.1.2. Male Subjects

Non-vasectomized male subjects with female partners of childbearing potential must be willing to use a condom from the time of the first dose of IP, during the clinical study and for at least 7 days after the last dose of IP, in addition to having their female partner use one of the following forms of contraception:

- Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation.
- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.

Sexual abstinence defined as refraining from heterosexual intercourse is considered a highly effective contraceptive measure only if it is the preferred and usual lifestyle of the subject. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study.

Periodic abstinence (e.g. calendar, symptothermal and post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only and lactational amenorrhea method are not acceptable methods of contraception.

In a case where the female partner of a male subject has undergone documented surgical sterilization that was performed more than one year before screening, then the subject is not required to use an additional form of contraception.

Vasectomized male subjects with female partners of childbearing potential are not required to use an additional form of contraception providing that surgical sterilization has been successful (documented azoospermia by semen analysis).

No sperm donation is allowed from the first dose of IP during the clinical study until 7 days after the last dose of IP.

6.3.2. Prior and Concomitant Medications

Prior and concomitant therapies taken for long term treatment of pre-existing conditions are allowed, provided they are in accordance with the inclusion and exclusion criteria (see Section 6.1 and Section 6.2, respectively) and with the prohibitions and restrictions listed below.

Information on previous inadequate response on MTX therapy for RA within 2 years prior to screening should be recorded with approximate dates of use (year, duration in months) and dose.

In case additional concomitant medications need to be administered or dose adjustments for pre-existing conditions (except for RA) are needed during the study, the risk/benefit to the subject should be carefully assessed by the study physician and consideration given to the timing of any necessary introduction of new medications.

If during the study, the subject's condition necessitates the use of prohibited medication, the use of IP may be interrupted, preferably after consultation with the sponsor's medical responsible. Re-introduction of IP can be considered after the treatment course with the prohibited medication has been stopped and after consultation with the sponsor's medical responsible.

During the study, subjects will be instructed to record any change in concomitant medication in a diary (see Section 8.8.1).

Permitted Medications

Permitted medications at screening and during the study include:

- NSAIDs, provided that the dose is stable for at least 2 weeks prior to first IP dosing and, if possible, is kept constant during the study.
- Analgesics, other than NSAIDs, up to the maximum recommended doses may be used for pain as required.
- Oral steroids, provided that the dose is stable, at a dose of ≤10 mg/day prednisone or equivalent (see Appendix 7 for prednisolone conversion table) for at least 4 weeks prior to first IP dosing, and is kept stable for the study duration.
- Medications prescribed for the treatment of comorbidities and which are not described as prohibited medications.

Prohibited Medications

Prohibited medications during the study include any DMARDs, other than background MTX, including:

- Oral or injectable gold, sulfasalazine, antimalarials, azathioprine, or D-penicillamine within 4 weeks prior to screening,
- cyclosporine within 8 weeks prior to screening,
- leflunomide within 3 months prior to screening or within 4 weeks prior to screening if after 11 days of standard cholestyramine therapy.

Current or previous treatment with a bDMARD. Except for subjects who received bDMARDs in a single clinical study setting:

- For whom the last dose of bDMARD ≥6 months prior to screening (12 months for rituximab or other lymphocyte depleting agents), AND;
- For whom the bDMARD was effective, without being discontinued due to lack of efficacy.

Previous treatment during the year before screening as well as during the study, with a cytotoxic agent other than MTX, is prohibited. These agents include, but are not limited to chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents.

Receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to screening is prohibited.

Other prohibited medications and dietary/herbal products:

The following medications should be discontinued at least 2 weeks or 5 half-lives of the drug, whichever is longer, prior to the first dose of IP administration and throughout the study.

- [redacted]

Additional guidance the use of concomitant medications:

- [redacted]

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The lists provided in Appendix 1 through Appendix 6 are non-exhaustive. In case of questions on concomitant medications, the sponsor's medical monitor (as per study contact list) and sponsor's medical responsible can be contacted.

6.3.3. Food and Beverage Restrictions

Subjects must come for the study visits, during the treatment and FU period, in the morning. At Visit 1, 3, 5, and if applicable the ED visit, subjects need to come for the study visits in a fasting state (no food intake for at least 8 hours).

Subjects will refrain from the consumption of grapefruit juice, grapefruit or Seville oranges beginning 48 hours prior to administration of the initial dose of IP, throughout the study until 7 days after the last IP administration.

6.4. Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal and Study Termination

A subject may be withdrawn from the clinical study at any time without the subject's consent if the investigator or sponsor determines that it is not in the best interest of the subject to continue participation. In such case, the reason for withdrawal will be documented in the source

documents, and the subject will be asked to complete the ED visit and FU visit for safety assessments.

Treatment with IP should be discontinued by the investigator (who may consult the sponsor's medical responsible) for any of the following conditions:

- Life-threatening adverse event (AE) or a serious adverse event (SAE) that places the subject at immediate risk.
- Serious infections deemed related to study treatment by the investigator, and requiring parenteral antimicrobial therapy and/or hospitalization.
- Confirmed pregnancy or lactation.
- Arrhythmia or conduction abnormality, including but not limited to prolonged QT interval corrected for the heart rate using Fridericia's formula (QTcF), where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (QTcF >500 ms on at least 2 separate ECGs) or clinically significant arrhythmia of any grade.
- Liver enzyme increase (see also Appendix 8)
  - AST and/or ALT ≥8x the ULN.
  - AST and/or ALT elevations ≥3x ULN with signs of liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥2.0x ULN or international normalized ration [INR] >1.5)
  - In addition, a dose interruption or reduction (if applicable) should be considered if AST and/or ALT ≥3x ULN and <5x ULN and dosing with IP should be interrupted if AST and/or ALT ≥5 and <8x ULN.
- Subjects presenting with signs and symptoms of SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and report an AE/SAE as applicable. In case of suspected SARS-CoV-2 infection RT-PCR and serology tests should be performed to confirm the infection. The investigator, preferably after consultation with the sponsor's medical responsible, must discontinue the subject from the study. The subject could be tested for SARS-CoV-2 in facilities outside the study site and if so, the subject should be instructed to immediately inform the study investigator if the test is positive and test results should be shared with the investigator as soon as possible.

  For subjects having:
  - AST or ALT ≥8xULN
  - AST or ALT ≥3xULN with signs of liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥1.5xULN or INR >1.5)

  The following steps will need to be performed by the investigator:

- The site should immediately contact the subject and require the subject to discontinue IP immediately. The subject should be asked to return to the site within a 48-hour window from awareness of the result.
- A full evaluation of various causes of hepatitis should be conducted (i.e. infectious, alcohol, medications, anatomical).
- An assessment of other concomitant medications and standard of care should be made. The investigator should consider whether it is in the best interest of the subject to stop/interrupt concomitant medications and standard of care treatment.
- A detailed history including relevant information on alcohol use, recreational drug use, supplement consumption, any herbal remedies, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, occupational history, blood transfusion, history of liver or allergic disease, and any other potential causes of attributable to a liver insult should be collected.
- A detailed assessment of the subject's clinical condition and repeat laboratory tests for liver function tests (LFT), including albumin, creatine kinase, total bilirubin (direct and indirect), gamma-glutamyl transferase (GGT), INR, and alkaline phosphatase should be done.
- Further testing for hepatitis A, B, and C, and for autoimmune hepatitis should be done. Other causes of viral hepatitis (cytomegalovirus or Eppstein Barr virus etc) should be excluded. Liver imaging should be considered.
- Referral to a hepatologist or gastroenterologist should be requested.
- All these cases should be reported as SAEs.

If during the study, the subject's condition necessitates the use of prohibited medication, the use of IP may be interrupted, preferably after consultation with the sponsor's medical responsible. Re-introduction of IP can be considered after the treatment course with the prohibited medication has been stopped and after consultation with the sponsor's medical responsible.

Every effort should be made to keep subjects in the study and on treatment. However, the investigator, who may consult the sponsor's medical responsible, can consider stopping the study treatment in case of concerns about the subject's safety, serious or severe AEs or worsening of the disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study (e.g. rescue medication). If IP treatment is interrupted due to an SAE, IP could be restarted, as per the investigator's judgment and after consultation with the sponsor's medical responsible.

When study treatment is discontinued, the subject will be requested to complete the assessments for the ED visit and return for the FU visit. Reason for discontinuation must be documented in the case report form (CRF).

Subjects will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a subject's participation in the clinical study may terminate at his/her request without prejudice to his/her future medical care. The subject will be encouraged to share the reason(s) for withdrawal so this can be documented in the source

documents, and to complete the ED visit and FU visit for safety assessments, but will not be obliged to do so.

Subjects who withdraw from the clinical study without contact with the site (lost-to-FU) should be contacted by the site so that their health status can be assessed and documented in the source documents. The site should make every effort to understand whether the subject is alive, including checking the medical records and contacting general practitioner or relatives, if necessary. All attempts must be documented in the source documents.

The sponsor has the right to terminate the clinical study at any time and for any reason. In this event, the investigator(s) and relevant authorities will be informed of the reason for clinical study termination.

6.5. Measures to Minimize Bias

6.5.1. Randomization

At screening, subjects will be assigned a subject identification number. When a subject is confirmed to be eligible for the clinical study, the subject will be randomized. Allocation of each subject to a given treatment will be done using a centralized electronic system (interactive voice/web response system [IXRS]). Subjects will be randomized in a 3:2 ratio to GLPG3970 or placebo.

6.5.2. Blinding and Unblinding

This is a randomized, double-blind clinical study. The subjects and the entire clinical study team, including the investigators, clinical study coordinators, and sponsor personnel are blinded to treatment assignment.

Blinded and packaged medication will be provided to the site. All IP formulations will be identical in appearance, shape, smell and taste, and will be packaged in the proper proportion to assure desired dosages and maintenance of the blinding.

The blind can be broken by the investigator for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the sponsor's medical responsible, whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary, but is required to inform the sponsor within 24 hours after unblinding has occurred.

The blind can be broken via IXRS by the investigator.

If the blind is broken for any reason during the course of the clinical study, the moment on which the blind was broken and all other relevant information will be documented by the site. The reason for breaking the blind will be indicated and justified in the source documentation.

If an AE leads to unblinding, the AE will be given as the reason for unblinding. All subjects who are unblinded should, where possible, complete the FU visit assessments 14±3 days after unblinding. Any AEs will be followed until resolution.

Code-breaking information (via IXRS vendor) will be provided to the bioanalytical laboratory responsible for plasma drug determination sample analysis, the person responsible for providing unblinded data to the Data Safety Monitoring Committee, the contract research organization (CRO) responsible for the population PK modeling, and to the sponsor pharmacovigilance vendor for SAE reporting purposes.

7. INVESTIGATIONAL MEDICINAL PRODUCTS

7.1. Identity of the Investigational Medicinal Product(s)

IP will be supplied to the pharmacist of the study site or to the hospital pharmacy, by and under the responsibility of the sponsor, who will also provide the investigator and pharmacist (or appropriate qualified member of the clinical study staff) with appropriate certificates of analytical conformity and European Union (EU) Qualified Person release documents.

For more details on the composition of the IP refer to the latest version of the IB and its relevant updates/addenda.

Detailed instructions on preparing and storing the IP will be provided to both the study site and the subjects.

7.2. Dosage and Administration

GLPG3970 will be provided as a powder and solvent to be reconstituted by the subject prior to use. The final dosage form for administration is an oral solution containing 400 mg of the active pharmaceutical ingredient G1567970 (G1567970 is the compound code for GLPG3970). A placebo powder and solvent for oral solution, to be reconstituted prior to use, will be also provided.

The IP needs to be taken q.d. at approximately the same time every morning on an empty stomach (i.e. IP intake should be at least 1 hour prior and at least 2 hours after a meal). At the baseline visit (Visit 1), IP will be administered on site after predose assessments have been completed. On visits 3, 4, and 5 subjects also need to take their IP on site. At Visit 1, 3, 5, and if applicable the ED visit, subjects need to come for the study visits in a fasting state (no food intake for at least 8 hours).

Subjects will receive powder and solvent to take home. The total content of the oral solution, reconstituted from the whole amount of powder and solvent, will need to be drunk. Detailed instructions for preparing and storing the applicable doses will be provided to the subject via on-site training on dummy kits and via a patient leaflet.

If a subject misses a dose (e.g. because he/she forgot to take the medication), he/she should take the missed dose within 12 hours after the planned intake time. If IP is not taken within 12 hours after the planned time, the missed dose should be skipped. For each dose taken at home, the time and date should be recorded in the subject's diary.

7.3. Packaging, Labeling and Distribution

IP packages will be labeled with clinical study-specific details, including storage conditions.

All manufacturing, packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Each medication kit will be identified with a unique kit number. Multiple kits can be provided to a subject at each visit, providing the subject with sufficient IP to cover the period until the next scheduled visit.

The distribution of IP to the site will only occur after the required local documentation is obtained, including clinical study approval by Competent Authorities and the IECs/IRBs, documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae), and the signed and dated study agreement and financial agreement.

To ensure study subjects maintain dosing per protocol requirements during this study special delivery services through DTP shipments of IP from the investigational site to the subject can be implemented in case of SARS-CoV-2 restrictions. DTP should only be used in case of emergency where on-site IP dispensation is not possible, and if allowed per local regulations. Local guidelines must be followed and regulatory approval or notification of authorities may be required. Agreement of the subject to receive IP at home is required prior to the shipment of IP from the investigational site to the subject's home. The DTP process used will be reviewed and approved by the sponsor, but the DTP shipments will be coordinated by the investigational site(s) in collaboration with the local CRO without the involvement of the sponsor to ensure clinical study integrity in case of SARS-CoV-2 restrictions.

7.4. Storage

Sites are to store IP supplies in a secure area until dispensed. Powder and solvent for oral solution at room temperature (below 30 °C), should not be refrigerated or frozen and protected from light and stored in the original packaging.

Sites will be required to monitor the storage temperature by using at least a min-max temperature-recording device and to keep a minimum to maximum temperature log, which must be completed each working day in order to establish a record of compliance with these storage conditions.

The investigator will instruct subjects on how the IP should be stored at home. Storage conditions to be taken into account by the subject when taking IP home, are described in the patient leaflet.

7.5. Treatment Compliance and Drug Accountability

The investigator should discuss treatment compliance with the subject prior to the start of the study. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure the proper subject dose. Subjects with poor compliance will be retrained by the site. IP administration as indicated by the subject (amounts as well as periods) will be recorded on the CRF.

The pharmacist or designated clinical study personnel will maintain a documentation of the total amount of IP received at site, amount dispensed to the subject, and the amount of IP returned by the subject to the site. IP supplies for each subject will be inventoried and accounted for throughout the clinical study. At the end of the treatment period, these records will be checked against the inventory by the study monitor. All clinical supplies will be stored in locked and access controlled facilities. Subjects will record IP administration at home in a subject diary.

Subjects will return any unused IP and empty IP packages at each study visit and/or ED visit. Upon sponsor approval, all unused IP and empty IP packages are to be returned from the sites and/or any vendor involved in the clinical study supplies management activities to the agreed location (depot), if possible. All returns and destruction must be properly documented.

8. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that CSP-required tests and procedures are completed as described in the Schedule of Activities (see Section 8.11). To avoid inter-observer variability, every effort should be made to ensure that all safety and efficacy evaluations are completed by the same individual who made the initial baseline determinations. In case study assessments are not performed for reasons related to SARS-CoV-2 pandemic restrictions, this should be documented in the medical records and e-CRF.
In case a randomized subject is not available to attend a scheduled study visit on site due to of SARS-CoV-2 travel restrictions, a phone call or a televisit may be conducted instead. It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow and the subject agrees, trained study staff or trained personnel are encouraged to collect study assessments at the study subjects' home or a local facility if social distancing and hygiene rules can be applied.
Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visit assessments and the alternative arrangements need to be adequately documented. Direct to patient shipments are possible if needed. Subjects presenting with signs and symptoms of infection, including SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and SARS-CoV-2 testing should be performed.

8.1. Timing of Assessments

The study assessments will be undertaken at time points as specified in the Schedule of Activities in Section 8.11. At Visit 1, 3, 5, and if applicable the ED visit, subjects need to come for the study visits in a fasting state (no food intake for at least 8 hours).

ICF needs to be signed before any study procedure, including screening procedure, is carried out.

The sequence of study assessments will preferably be as follows when planned at the same time point:

1. Patient Questionnaires: Patients's Global Assessment of Disease Activity and Patient-Reported Functional Status and Pain
2. Investigator Questionnaires and joint counts
3. 12-Lead ECG
4. Vital signs
5. Blood sampling for clinical laboratory assessments and PK

[redacted]

The following collection time windows apply:

- 12-Lead ECGs, vital signs and physical examinations: within 3 hours predose.
- Urine sampling for clinical laboratory safety: any time predose, on the same visit day, and 2 hours postdose on visits 1 and 5.
- [redacted]
- Blood sampling for PK determination of GLPG3970:
  - Visit 1, 3, 4 and 5: within 30 minutes predose.
  - Visit 1: 1 sample within [0.5-1.5 hours postdose] and 1 sample within [2-2.5 hours postdose].
  - Visit 5: 1 sample within [4-6 hours postdose].
- [redacted]

8.1.1. Retesting During Screening

During the screening period, one retest of the following assessments is allowed:

- For resting pulse (after 5 min seated position).
- For re-evaluation of active joints and DAS28 score for defining moderate to severely active RA.

- For QuantiFERON –TB Gold test with indeterminate result (the subject is not eligible if retest result is indeterminate or positive).
- During screening or later during the study, retesting (resampling) of clinical laboratory safety tests or SARS-CoV-2 RT-PCR tests is allowed once, only for technical or transport reasons (e.g. sample hemolyzed, out of stability, late arrival at laboratory impacting sample quality, loss, or destruction of the sample before analysis).

8.1.2. Rescreening of Subjects

If a subject is a screening failure, it is allowed to rescreen the subject once, if the reason for failure is temporary and expected to resolve, as judged by the investigator. When a subject is rescreened, the subject needs to be reconsented and all screening assessments need to be repeated. The subject will be assigned a new subject identification number. The time in between 2 screening attempts could vary depending on the screening failure reason.

The following data will be collected for screening failure subjects: ICF signed data, demographics, failed inclusion or exclusion criteria, and AEs.

8.2. Unscheduled Visits

Additional visits can be performed at other time points for any safety assessments, if clinically indicated. These unscheduled visits and outcomes of additional assessments need to be recorded in the source and, if performed before the subject's last visit per CSP, also in the CRF.

8.3. Initial Subject and Disease Characteristics

Subjects will be asked to attend the study site for a screening assessment. After giving written informed consent, demographic data (year of birth, age, sex, ethnicity and race) will be collected and medical history will be taken, including RA disease history and treatment history. RA disease history will capture the duration of disease, clinical symptoms, and medication used to treat the disease. A physical examination will be performed, including measurement of weight and height. The subject's diagnosis of RA will be confirmed based on 2010 ACR/EULAR criteria (documented diagnosis) and classified as ACR functional class I-III.

Vital signs (systolic and diastolic blood pressure, pulse, oral/tympanic body temperature, the same method of measuring body temperature to be used throughout the study) will be measured and a 12-lead ECG will be recorded. Subjects should rest for at least 5 minutes in the supine position before the ECG recording, blood pressure and pulse measurement.

The inclusion and exclusion criteria will be checked to assess eligibility for the study. All screening tests will be reviewed to confirm eligibility before randomization and the first IP dose.

A serum pregnancy test will be done for all female subjects as well as an FSH test for postmenopausal female subjects.

8.4. Efficacy Assessments

8.4.1. Joint Counts

On the visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"), each of 68 joints will be evaluated for tenderness (tender joint count, TJC68), and each of 66 joints will be evaluated for swelling (swollen joint count, SJC66) (Appendix 9).

A joint assessor with adequate training and experience in performing joint assessments will be designated at each study site to perform all joint assessments. The joint assessor should preferably be a rheumatologist, however, if a rheumatologist is not available, it should be a health care worker with at least one year's experience in performing joint assessments. The assessor should remain the same throughout the study per subject, as much as possible. It is required that the designated joint assessor identifies an appropriate back-up assessor to provide coverage if the designated joint assessor is absent.

8.4.2. [redacted]

[redacted]

8.4.2.1. [redacted]

[redacted]

8.4.2.2. [redacted]

[redacted]

8.4.3. [redacted]

[redacted]

[redacted]

8.5. Safety Assessments

This section describes methods and timing for all safety assessments and recording. Additional assessments (e.g. unscheduled clinical laboratory tests or extra vital signs recordings) are allowed to ensure appropriate collection of safety data and to assess any perceived safety concerns.

8.5.1. Adverse Events

The AEs reporting period for safety surveillance begins when the subject signs the ICF and ends at his/her last FU visit.

Detailed definitions, ratings and reporting requirements for AEs and SAEs are found in Section 11.

8.5.2. Clinical Laboratory Evaluations

The following clinical laboratory safety tests will be performed:

- **Hematology:**
  hematocrit, hemoglobin, red blood cell count, white blood cell count, white blood cell differential count (absolute and relative), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width and platelets.
- **Coagulation:**
  INR (only when increase in LFTs, see Section 6.4), activated partial thromboplastin time and prothrombin time.
- **Clinical chemistry:**
  glucose, urea, creatinine, uric acid, sodium, potassium, calcium, reflex calcium (free/ionized; only if serum calcium total is elevated), chloride, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase (ALP, ALP fractions only if ALP is elevated), creatine phosphokinase, lipase, amylase, lactate dehydrogenase, insulin, hemoglobin A1c (HbA1c), albumin, total proteins, triglycerides, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and hsCRP.
  Homeostatic model assessment of insulin resistance (HOMA-IR, see Definition of Terms) and HDL/LDL ratio will be derived from clinical chemistry parameters. An estimate of the

ClCr based on the serum creatinine level will be calculated by the central laboratory using the Cockroft-Gault formula (see Definition of Terms).

- **Urinalysis:**
  Dipstick: pH, glucose, proteins (qualitative), blood, leukocytes, ketones.
  Microscopic examination of the sediment for cellular elements (cylinders, erythrocytes, leukocytes), if indicated (when the test strip was positive for blood and/or proteins).
  Quantitative urine proteins, only when the test strip was positive for proteins.
  Calcium, phosphate, creatinine and N-acetyl-β-D-glucosaminidase (NAG). The urine protein to creatinine ratio will be derived.
- **Serology:**
  HBsAg and hepatitis C antibody, and HIV 1 and 2 (at screening). Positive hepatitis and HIV results should be reported by the investigator as required by local law.
- FSH test for females at screening to confirm menopause if applicable
- **Pregnancy test for females:**
  serum beta human chorionic gonadotropin at screening, baseline (Visit 1), at Visit 4 (Day 29) and at Visit 5 (Day 43), , or the ED visit, if applicable (all female subjects).
- **QuantiFERON-TB Gold test** to check for latent or active TB (at screening). TB results should be reported by the investigator as required by local law.
- **SARS-CoV-2:**
  RT-PCR from a nasal swab sample to check for SARS-CoV-2 infection at screening and RT-PCR from a nasal swab sample and serology testing at baseline, and throughout the study as needed (when SARS-CoV-2 symptoms present).

The clinical laboratory evaluations will be performed at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Reference ranges will be supplied by the central laboratory. Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Only laboratory test abnormalities judged as clinically significant by the principal investigator should be recorded as AEs.

The details of blood and urine sample handling and shipment instructions will be provided in a separate laboratory manual.

8.5.3. Physical Examination

Physical examinations will be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Height and weight will also be measured at visits specified in the Schedule of Activities in Section 8.11. The person conducting the physical examination will document this in the subject's medical records. Clinically significant abnormal findings should be recorded as AEs.

Particular attention should go to physical examination at all visits, to identify any potential SARS-CoV-2 related signs and symptoms, indicating potential infection (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, others). Subjects

presenting such symptoms at screening/baseline should not be included/randomized in the study (see Section 6.2). Developing such symptoms during the study, should be managed as per Section 8.5.6.

8.5.4. Vital Signs

Vital signs (systolic and diastolic blood pressure taken at the same arm for each measurement, pulse and oral/tympanic body temperature, the same method of measuring body temperature to be used throughout the study) will be recorded in a standardized manner (i.e. after the subject has rested in a supine position for at least 5 minutes) at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Clinically significant abnormal values should be recorded as AEs.

8.5.5. 12-lead Electrocardiogram

At the time points specified in the Schedule of Activities (see Section 8.11 and also Section 8.1, "Timing of Assessments"), a triplicate 12-lead ECG will be recorded and results will be sent for central reading.

12-lead ECG recordings will be performed before blood sampling and after subjects rested for at least 5 minutes in supine position. In case an indwelling catheter is used, ECGs may be recorded after blood sampling, provided that there is at least 30 minutes between catheter insertion and the ECG recording. When catheter insertion would fail, the 12-lead ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt. Triplicate ECGs will be performed within a time span of 10 minutes, with an approximate 3-minute interval between ECGs.

The following parameters need to be recorded: heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, morphology and rhythm analysis (QTcF will be derived). QTcF will be considered as normal if ≤450 ms (male) and ≤460 ms (female), while a prolongation of QTcF to >500 ms or an increase from baseline >60 ms will be considered a threshold of concern.

Immediately after recording, the ECG will be reviewed by the investigator on clinical significant abnormalities. This immediate review during the visit needs to be documented in the subject's source. After receipt of the central report, also all flagged ECG abnormalities need to be assessed by the investigator on clinical relevance. Clinically significant abnormal findings should be recorded as AEs.

8.5.6. Other Safety Assessments

SARS-CoV-2 infection will be assessed at screening by RT-PCR and at baseline through careful physical examination to exclude any potential signs and symptoms of infection, e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, etc.

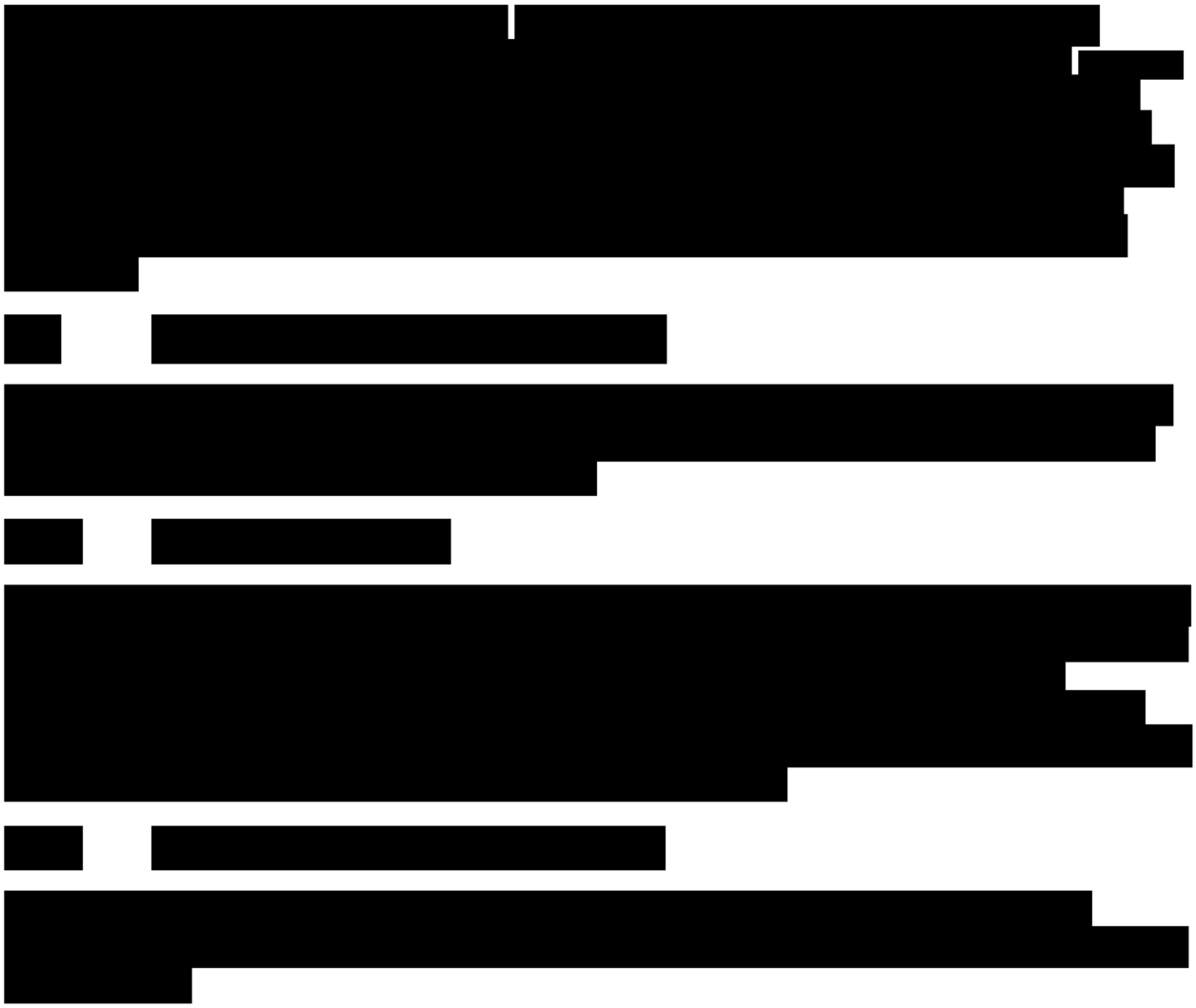
Additional RT-PCR and serology testing will be repeated at baseline for documentation and throughout the study as needed. The subject could be tested for SARS-CoV-2 in facilities outside the study site and if so, the subject should be instructed to immediately inform the study

investigator if the test is positive and test results should be shared with the investigator as soon as possible.

On Day 8, subjects should be contacted by the site via a telephone call. The site should remotely check the overall status of the subject and review safety related information, if applicable, both in the context of the clinical study and linked to the SARS-CoV-2 pandemic.

8.6. Pharmacokinetic Assessments

Blood samples for the PK assessment of GLPG3970 should be collected on the visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Samples will be obtained by venipuncture (or indwelling cannula), preferably in the forearm into tubes containing K2EDTA and will be immediately chilled (ice bath). Within 30 minutes after blood collection, the plasma will be separated in a refrigerated centrifuge at 4 °C for 10 minutes at circa 1500 g and transferred into tubes as described in the laboratory manual. The plasma samples will be stored at -60 °C or below at the site until shipment to the bioanalytical laboratory.



[redacted]

8.8. Other Assessments

Not applicable.

8.8.1. Subject Diary

At visits specified in the Schedule of Activities (Section 8.11) a diary and instructions for completion will be provided. The subjects will record on a daily basis any changes in concomitant illnesses, new AEs, exposure to individuals with confirmed or suspected diagnosis of SARS-CoV-2 infection, any change in concomitant medication, date and time of IP and MTX intake, and whether IP intake was done on an empty stomach (i.e. 1 hour prior and at least 2 hours after a meal) throughout the study (from signature of ICF until the FU visit). An automated alert system will notify the investigator and sponsor of any signs or symptoms or information possibly related to SARS-CoV-2 that is entered by the subject in the diary.

Subjects will be trained on how to complete the subject diary.

8.9. Sample Management

The total amount of blood to be taken per subject over a period of 11 weeks, for scheduled safety laboratory parameters and PK [redacted] assessments, will not exceed approximately [redacted] mL.

Blood and Urine Samples for Routine Safety Tests, Serology, FSH and Pregnancy Tests

All blood and urine samples for routine safety tests, serology, FSH and pregnancy tests will be analyzed in a central laboratory and will be destroyed after analysis.

Blood Samples for PK and [redacted]

After the end of the study (defined in Section 5.2), all biological samples obtained during the clinical study may be stored for a maximum period of 5 years, after which the samples will be destroyed. The sample storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g. health authority requirements).

The stored samples shall only be used by the sponsor, sponsor partners and/or other companies contracted by the sponsor, for research related to this clinical study. Any research outside the context described in this CSP may only be conducted after approval by the IRB/IEC and Regulatory Authority and after obtaining informed consent from the subject.

[redacted]

8.10. [redacted]

8.11. Schedule of Activities

For detailed instructions on the clinical study procedures, please see referred sections and Section 8.1, "Timing of Assessments".

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
On site visit	✓	✓		✓	✓	✓	✓	✓
Telephone call			✓					
Informed consent	✓							
Inclusion/exclusion criteria	✓	✓						
Demographics	✓							
Medical history	✓							
FSH test (postmenopausal women)	✓							

[1] On dosing days, all assessments are to be performed within 3 hours pre-dose, unless otherwise specified.
[2] Subjects must come for the study visits 1, 3 and 5 in the morning in a fasting state (no food intake for at least 8 hours). For Visit 1 (predose measurements) and for 2 post dose visits (Visit 3, 4 or 5) all attempts should be made to plan the visit within 2 days following MTX intake.
[3] Subjects who discontinue treatment early will be requested to return for an early discontinuation (ED) visit to complete all Visit 5 assessments and to return for a follow-up (FU) visit 14 ± 3 days after last IP administration.

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
Pregnancy test[4]	✓	✓			✓	✓	✓	
Physical examination	✓	✓				✓	✓	✓
Vital signs	✓	✓		✓	✓	✓	✓	✓
Body weight and height [5]	✓	✓		✓	✓	✓	✓	✓
12-lead triplicate ECG	✓	✓		✓	✓	✓	✓	✓
Serology	✓							
QuantiFERON-TB Gold test	✓							
SARS-CoV-2 RT-PCR test[6]	✓	✓	As needed					
SARS-CoV-2 serology test[6]		✓	As needed					
Randomization		✓						
Clinical safety blood samples	✓	✓[7]		✓[7]	✓	✓[7]	✓	✓

[4] Serum beta human chorionic gonadotropin at screening, baseline (Visit 1), Visit 4 and Visit 5, or at the ED visit, if applicable (all female subjects).
[5] Height only to be measured at screening.
[6] RT-PCR from a nasal swab sample at screening and RT-PCR from a nasal swab sample and serology testing at baseline (Visit 1), and as needed when subject presents signs and symptoms of SARS-CoV-2 infection.
[7] Fasted glucose, fasted insuline and HOMA-IR only at Visit 1, 3 and 5 and the ED visit, if applicable.

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
Clinical safety urine samples [8]	✓	✓[9]		✓	✓	✓[9]	✓	✓
PK blood samples for GLPG3970		✓[10]		✓[11]	✓[11]	✓[11,12]	✓	
[redacted]		[redacted]		[redacted]	[redacted]			
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]				[redacted]	[redacted]	
Subject diary evaluation		✓	✓	✓	✓	✓	✓	✓

[8] On dosing days, clinical safety urine samples will be taken predose, on the same visit day.
[9] Visit 1 and 5: predose and 2 hours postdose. Calcium and phosphate should only be evaluated at Visits 1 and 5.
[10] Visit 1: predose (within 30 minutes prior to dosing), 1 sample within [0.5-1.5 hours postdose] and 1 sample within [2 – 2.5 hours postdose].
[11] Visit 3, 4 and 5: predose (within 30 minutes prior to dosing).
[12] Visit 5: 1 sample within [4-6 hours postdose].
[13] [redacted]

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1],[2]						FOLLOW-UP PERIOD[2]
Study visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[3]**	**FU Visit**
Study Weeks		**Baseline**	**1**	**2**	**4**	**6**		
Study Day (D) ± Days	**-21 to -1**	**1**	**8 ± 2**	**15 ± 2**	**29 ± 2**	**43 ± 2**	**Early treatment discontinuation**	**57 ± 3**
SJC66/TJC68	✓	✓		✓	✓	✓	✓	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dispense IP		✓[15]		✓[15]	✓[15]			
IP administration [15]		Once daily throughout the treatment period						
AE and concomitant medication	throughout the study							

[15] On Visit 1, 3, 4 and 5 administration of IP must occur at site.

9. STATISTICAL METHODS

All statistical methods shall be detailed in a statistical analysis plan (SAP) that will be finalized prior to the database lock and unblinding. All relevant data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

Any deviations from the CSP are to be justified in the SAP.

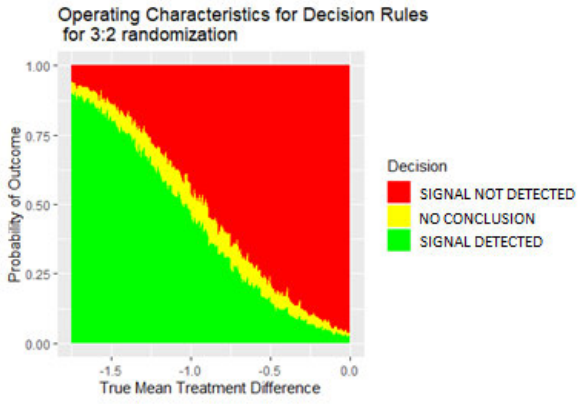
9.1. Determination of Sample Size

The operating characteristics of the chosen decision framework at a sample size of 15 subjects (GLPG3970) + 10 subjects (placebo) are represented in the following graphical output and table, and were deemed acceptable. A common standard deviation (SD) of 1.3 for placebo and GLPG3970 was assumed based on previous experience with RA studies.

Lower Reference Value and Target Value for the decision framework were determined based on the published studies and the therapies in development or on the market. They were identified by the project team as the lowest delta of possible interest and the best case scenario for efficacy outcome respectively.

A dropout rate of 20% was taken into account to allow a minimum of 20 subjects to complete the study. In case of drop-outs due to SARS-CoV-2 infection, additional subjects may be randomized on top of the planned sample size. The number of additional subjects randomized will not exceed the number of subjects dropping out of the study in relation to SARS-CoV-2. Randomization of additional subjects will ultimately be decided by the sponsor before any study lock or related unblinding has occurred.

Probability	Reference value	Outcome
0.852	-1.6	Signal detected
0.043	-1.6	No conclusion
0.105	-1.6	No signal detected
0.192	-0.6	Signal detected
0.091	-0.6	No conclusion
0.717	-0.6	No signal detected



9.2. Population for Analyses

9.2.1. All Screened Subjects

All subjects who signed and dated an ICF.

9.2.2. All Randomized Subjects

All screened subjects who were randomized into the clinical study.

9.2.3. Full Analysis Set

All randomized subjects who have received/used at least 1 dose of IP.

9.2.4. Safety Analysis Set

All subjects who used at least 1 dose of IP.

9.2.5. Pharmacokinetic Analysis Set

Subset of the Safety Analysis Set for which plasma concentration data are available to facilitate development of the Population PK model as described in the pharmacometric analysis plan and excluding CSP deviations which have an impact on the PK analysis.

9.2.6. [redacted]

[redacted]

9.2.7. Pharmacokinetic/[redacted]

Intersection of the PK and [redacted].

9.3. Statistical Analyses

9.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, SDs and/or standard error (as appropriate), median, minimum and maximum (for continuous variables), and the number and percentage per category (for categorical data). In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data.

Baseline is defined as the last available assessment prior to the first intake of IP. For ECG, the baseline ECG result is the mean of the last available triplicate prior to the first intake of IP.

Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 10% significance level. Data may be pooled across centers and countries.

9.3.2. Interim Analysis

No formal interim analysis is planned for this clinical study.

9.3.3. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for ED), CSP deviations, demographics, baseline characteristics, medical history, and concomitant therapies will be analyzed descriptively

9.3.4. Analyses of Efficacy Parameters

Efficacy analyses will be performed on the Full Analysis Set.

9.3.4.1. Analysis for Primary Efficacy Endpoint

A mixed model for repeated measures (MMRM) will be used on the DAS28 (CRP) changes from baseline to compare treatment groups, with a 90% confidence interval (CI) of the treatment difference at Week 6.

Secondly, the signal detection methodology described by Frewer et al (Frewer, Mitchell, Watkins, & Matcham, 2016). will be used to provide further insight into the treatment effect of GLPG3970 over placebo, and will support scenario analyses. The posterior distribution of this treatment effect will be estimated, and from this distribution probabilities of reaching at least a certain effect (delta) will be derived, e.g. a range of plausible effect size values going from as high as P (delta $\leq$ -1.6) to as low as P (delta $\leq$ -0.6).

The chosen framework is as follows:

- Target value (TV): -1.6 and lower reference value (LRV): -0.6
- False stop risk: 20% and false go risk: 10%
- Framework rules:
    - Signal detected if P10 < TV and P80 < LRV
    - No signal detected if P10 $\geq$ TV
    - No conclusion if P10 < TV

9.3.4.2. [redacted]

[redacted]

9.3.5. Analyses of Safety Data

All safety analyses will be performed using the Safety Analysis Set (Section 9.2.4). All safety data collected on or after the first dose of IP administration up to the last contact after the last dose of IP, unless specified otherwise, will be summarized by treatment group according to the IP

received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

9.3.5.1. Extent of Exposure

A subject's extent of exposure to the IP will be generated from the IP administration page of the CRF. Exposure data will be summarized by treatment group. Duration of exposure to the IP will be expressed as the number of days between the first and last dose of IP, inclusive, regardless of temporary interruptions in IP administration and summarized by treatment group.

9.3.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. System Organ Class (SOC), High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

The following AEs will be considered as TEAEs:

Any AE with an onset date on or after the IP start date and no later than 14 days after last dose of IP, or any worsening of any AE on or after the IP start date. Investigators are not obliged to actively seek SAEs after the CSP-defined FU period. However, if the investigator is informed about an SAE that occurs at any time after the subjects post-treatment FU visit and the event is deemed relevant to the use of IP, they should promptly document and report the event to the sponsor by using the SAE form.

Summaries (number and percentage of subjects) of TEAEs per subject by SOC and Preferred Term will be provided by treatment group. TEAEs will also be summarized by causal relationship to the IP and severity. In addition, TEAEs leading to ED of the IP will be summarized and listed. Also, all SAEs, including the non-treatment-emergent SAEs, will be listed.

9.3.5.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline and treatment-emergent shifts, according to normal ranges as well as CTCAE version current at the time of the assessment, will be presented. Analyses will be done per treatment group.

9.3.5.4. Physical Examinations

Only abnormal post-baseline physical examination results will be listed, when available.

9.3.5.5. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline will be presented as well. Analyses will be done per treatment group.

9.3.5.6. 12-Lead Electrocardiogram

A descriptive analysis will be done for the 12-lead ECG. Changes from baseline (Day 1 predose) will be presented as well. Frequency analyses of abnormalities based on actual values and on changes from baseline will be presented as well. Analyses will be done per treatment group.

9.3.6. Pharmacokinetic Analyses

Descriptive statistics will be done on C_{trough} plasma levels for GLPG3970. [redacted]

Observed GLPG3970 plasma concentrations will be analyzed using a population PK approach to characterize the PK profile of GLPG3970. [redacted]

9.3.7. CI [redacted]

[redacted]

9.3.8. Additional Statistical Considerations

Not applicable.

10. DATA MONITORING

10.1. Data Safety Monitoring Committee

An Internal Data Safety Monitoring Committee independent from the study will review unblinded data during the course of the study. This Committee may involve external medical

experts (such as an expert in the field of RA and an infectious diseases expert) to support data interpretation. The Committee will review unblinded safety data and assess any potential safety issues arising during the conduct of the clinical study, including (but not limited to) any potential issues in the context of the SARS-CoV-2 pandemic. The process is described in a separate 'Internal Safety Monitoring Committee Charter'.

11. SAFETY REPORTING

11.1. Definitions of Adverse Events, Serious Adverse Events and Special Situations

11.1.1. Adverse Events

An AE is any untoward medical occurrence, new or worsening of any pre-existing condition, in a clinical study subject administered a medicinal 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 (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related. AEs may also include pre- or post-treatment complications that occur as a result of CSP-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing conditions that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

11.1.2. Serious Adverse Events

An SAE is defined as an AE that:

- Results in death;
- Is life-threatening (Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly / birth defect;
- Is medically significant (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above).

11.1.3. Unlisted (Unexpected) Adverse Events/ Reference Safety Information

An AE is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For an IP, the expectedness of an AE will be determined by whether or not it is listed in the reference safety information part of the IB.

11.1.4. Adverse Events of Special Interest

Not applicable.

11.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance based on the investigator's judgment are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) or other abnormal (clinical study-specific) assessments (e.g. ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, and/or lead to IP interruption, modification or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 11.1.1 and 11.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

The following liver enzyme elevations should be reported as SAEs:

- AST or ALT ≥8xULN.
- AST or ALT ≥3xULN with signs of liver damage (total bilirubin >2xULN OR international normalized ratio >1.5, and/or with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%]).

11.1.6. Special Situations

Special situations are situations that have a possible impact on the safe use of the IP. These situations might be or might not be associated with AEs.

- Pregnancy
- Abuse or misuse of IP
  Abuse of IP is defined as the persistent or sporadic, intentional excessive use of the IP, which is accompanied by harmful physical or psychological effects.
  Misuse of IP is defined as a situation where the IP is intentionally and inappropriately used not in accordance with the product information.
- Drug interaction or food interaction with IP
  A drug interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with another drug when both are administered together.
  A food interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with a food when taken together.
- Medication error with IP

A medication error with IP is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.

- Occupational exposure to IP
  Occupational exposure to IP is defined as an exposure to the IP as a result of one's professional or non-professional occupation.
- Overdose with IP
  An overdose of IP is defined as the administration of a quantity of the IP given per administration or cumulatively, which is above the dose of IP given during this study.
- Product complaint or quality defect of IP
  Product complaint or quality defect of IP is defined as complaints or defects of the IP arising from potential deviations in the manufacture, packaging, or distribution of the IP.

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator is responsible for assessing AEs and SAEs for causality and severity. This is the basis for the sponsor's final review and confirmation of accuracy and completeness of event information and causality assessments.

11.2.1. Assessment of Causality

The investigator is responsible for assessing the causal relationship to IP(s) administration or study procedures (e.g. invasive procedures such as venipuncture) based on her/his clinical judgment. The following decision choice will be used by the investigator to describe the causality assessment between the reported event or laboratory test abnormality and the IP.

- **Unrelated:**
  Time relationship to IP intake is improbable. Related to other etiologies such as concomitant medications or subject's clinical state.
- **Unlikely:**
  Time relationship to IP intake is improbable (but not impossible). Concomitant disease or other drugs provide plausible explanations.
- **Possible:**
  Time relationship to IP intake is reasonable. Event or laboratory test abnormality could also be explained by disease or other drugs. Information on IP withdrawal may be lacking or unclear.
- **Probable:**
  Time relationship to IP intake is reasonable. Unlikely to be attributed to concurrent disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.

– **Certain:**
Time relationship to IP intake is plausible. Cannot be explained by concomitant disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if ethical and necessary.

It should be emphasized that ineffective treatment (worsening of the disease) should not be considered as causally related in the context of AE reporting.

11.2.2. Assessment of Severity

The severity of AEs should be graded using the CTCAE version current at the time of assessment. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in the table below.

Table 1 Grading of AE Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death-related AE
*	Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.	
**	Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. This is upon the investigator's assessment.

If there is a change in intensity (worsening or improvement) of an AE, it must be recorded.

11.2.3. Action Taken Regarding Investigational Product

The action taken must be described by choosing from:

- Dose not changed: In case no action is taken regarding the IP.
- IP permanently discontinued: In case a subject is permanently discontinued from treatment or withdrawn from the study by the investigator (who may consult the sponsor's medical monitor).
- IP temporarily discontinued: In case the IP is temporarily discontinued by the investigator (who may consult the sponsor's medical monitor).
- Not applicable: Other situations (e.g. in case an AE started after the last IP administration).

11.2.4. Outcome

Each AE must be rated by choosing among:

- Recovered/resolved;
- Recovered/resolved with sequelae;
- Recovering/resolving;
- Not recovered/not resolved;
- Fatal;
- Unknown.

11.3. Investigator Requirements and Instructions for Reporting Adverse Events, Serious Adverse Events, Pregnancies, and Other Special Situations to the Sponsor

11.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's last FU visit (the last FU visit after the last dose of IP). In this period, all new AEs, regardless of cause or relationship, derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as "How do you feel?") need to be recorded in the source and in the CRF.

In case an AE is ongoing at the time of the last FU visit, the investigator needs to FU on the subject until AE resolution or reasonable stabilization and to document in the subject's source documentation. No related updates or additional data on the AE should be reported in the CRF.

If a subject is documented as lost-to-FU, ongoing/unknown outcome AEs will not be followed-up.

If the AE meets the criteria for seriousness, the SAE form must be completed and sent to the sponsor within 24 hours (see Section 11.3.2).

11.3.2. Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The subject will remain under observation as long as medically indicated. Appropriate laboratory tests will be performed until all parameters return to normal or are otherwise explained or stable.

All SAEs, whether or not deemed IP related, must be recorded in the CRF and on the SAE form. The investigator must report each SAE immediately, and under no circumstances should this exceed 24 hours following the knowledge of the SAE, as is indicated on page 2 under "Emergency Contact Information".

The SAE form should at least contain identifiers of the subject and the reporter, SAE term and statement of relatedness to the IP, and at a later stage if not yet available within 24 hours, the form needs to be completed with a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae.

Follow-up and outcomes should be reported and documented in the source documents for all subjects that experience an SAE. It is important that the information provided on the SAE form matches the information recorded on the CRF for the same event.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and available. Only subject identifiers (subject number) should appear on the copies, and all names and initials should be blackened and rendered illegible. Follow-up reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Any SAEs that occur after the post-treatment FU visit but within 30 days of the last dose of IP(s), regardless of causality, should also be reported (Emergency Contact Information on page 2). Investigators are not obligated to actively seek SAEs after the CSP-defined FU period. However, if the investigator is informed about an SAE that occurs at any time after the subjects' post-treatment FU visit and the event is deemed relevant to the use of IP(s), he/she should promptly document and report the event to the sponsor by using the SAE form.

11.3.3. Pregnancy

All initial reports of pregnancy in female subjects and pregnancies in partners of male subjects included in the clinical study must be recorded and documented in the source documents and on the pregnancy form. The investigator must report each pregnancy immediately, and under no circumstances should this exceed 24 hours following the knowledge of the pregnancy, as is indicated on page 2 under "Emergency Contact Information".

All pregnancies should be followed-up until delivery or pregnancy interruption. The investigator will contact the subject or partner of the subject after giving consent, at the expected time of delivery for FU and for information regarding the outcome of the newborn. Abnormal pregnancy

and/or abnormal newborn outcomes are considered SAEs and must be reported using the SAE form.

11.3.4. Reporting of Special Situations (Other Than Pregnancy) and Associated Adverse Events

In case a special situation is not associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form as is indicated on page 2 under "Emergency Contact Information".

In case a special situation is associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form and the associated AE should be reported as specified in Section 11.3.1.

In case a special situation is associated with an SAE, the special situation should be reported within 24 hours by using the SAE form (and not the Special Situations form) and the associated SAE should be reported as specified in Section 11.3.2.

11.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States Federal Drug Administration Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, the sponsor may be required to expedite reports of SAEs and serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs) to worldwide regulatory authorities. The sponsor or a specified designee will notify worldwide regulatory authorities and the relevant IEC/IRB in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined using the reference safety information section in the IB or relevant local label as applicable.

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any IP(s). The investigator should notify the IEC/IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

12. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This clinical study is conducted in accordance with the current applicable regulations, ICH-GCP Guideline E6 and its updates, and local ethical and legal requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of clinical study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

The name and address of each third party vendor (e.g. CRO) used in this study and the sponsor's study team members will be maintained in the investigator's and sponsor's files as appropriate.

12.1. Sponsor's Responsibilities

12.1.1. Regulatory Authority Approval

Prior to clinical study start, this CSP together with all relevant documentation needs to be submitted to the respective regulatory authorities for review and approval in compliance with current regulations before the study can start.

12.1.2. Clinical Study Closure Considerations

The sponsor reserves the right to close the investigational site or end the clinical study at any time for any reason. In case of an early termination of the clinical study or temporary halt by the sponsor, the IEC/IRB and health authority will be notified within 15 calendar days, unless otherwise specified by the sponsor, the IEC/IRB or health authority, including a detailed written explanation of the reasons for the termination/halt.

Reasons for the closure of an investigational site may include, but are not limited to:

- Successful completion of the clinical study at the center.
- The overall required number of subjects for the clinical study has been recruited.
- Failure of the investigator to comply with the CSP, ICH-GCP guidelines or local requirements.
- Inadequate recruitment of subjects by the investigator.

Reasons for early termination of a clinical study by the sponsor may include, but are not limited to:

- Safety concerns.
- Sufficient data suggesting lack of efficacy.

The end of clinical study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete clinical study has ended in all participating centers, in all countries. This notification will also be submitted according to local requirements of the end of the clinical study in a given country/member state.

12.1.3. Indemnification

Under the conditions of a contract concluded between investigator, site and sponsor or designee, which shall prevail, the sponsor shall, except in case of gross negligence or willful misconduct, indemnify and hold harmless the investigator and his/her medical staff from any claim arising from the clinical study activities carried out in compliance with the CSP, sponsor's instructions and applicable local regulations.

The investigator must notify the sponsor immediately upon notice of any claims or lawsuits.

12.1.4. Insurance

The sponsor shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Provided that the subject has been treated according to the CSP and sponsor's instructions, any injury caused to a subject which is the direct result of his/her participation to the clinical study shall be covered by the sponsor's insurance, except in case of gross negligence or willful misconduct by the investigator.

12.1.5. Archiving

The sponsor will archive the content of the Trial Master File (TMF) for at least 25 years after the end of the clinical study.

12.1.6. Reporting

Where required by IEC/IRB per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study (see Section 12.4.1). At the end of the clinical study, the results of the clinical study will be reported in a CSR. The pop-PK analysis data, disease and/or drug-related biomarker data and mRNA data may be reported separately from the main CSR. A summary or full report, depending on the requirements, will be provided to the investigators, to the applicable regulatory authorities, and IECs/IRBs (if required by the applicable regulatory requirements) within one year, or 6 months for pediatric studies, after the end of the clinical study.

12.1.7. Publication

It is understood by the investigator that the sponsor shall be free to use the compound-related information, which is generated during the clinical study and may disclose it to other clinical investigators and to regulatory agencies. As a consequence, the investigator agrees to provide all clinical study results and data generated during this clinical study to the sponsor.

The investigator shall not be authorized to submit the results of this clinical study and any data for public disclosure (e.g. publication or presentation) without the prior written approval of the sponsor, which shall not be unreasonably withheld.

However, it is understood and agreed by the investigators that their results and/or findings shall not be authorized for publication prior to sponsor's publication of the overall clinical study results. The investigator agrees that prior to the publication of any results, he/she shall provide the sponsor with a draft copy of the intended publication. The sponsor shall have the right to review it and to make any comments. In accordance with generally accepted scientific collaboration principles, co-authorship with any staff member sponsor involved in the clinical study, will be discussed and mutually agreed upon before submission of any manuscript to a publisher.

12.2. Investigator's Responsibilities

12.2.1. Source Data and Data Capture

The nature and location of all source documents need to be identified and documented to ensure that all sources of original data required to complete the CRF are known and are accessible for verification by the monitor.

Source data may be directly captured from devices transferred from third partners (e.g. laboratory data) or entered manually into the CRF. The CRF completion guidelines will be provided to each investigational site.

It is recommended that the author of an entry in the source documents should be identifiable. Following ICH-GCP guidelines, direct access to sponsor's representatives to source documents must be granted for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

12.2.2. Archiving

Unless local legislation requires archiving for a longer period, the investigator shall archive the content of the clinical investigator site file (ISF) for at least 25 years after the end of the clinical study. However, the medical files of subjects shall be archived in accordance with national law.

The investigator should take measures to prevent accidental or premature destruction of these documents.

Under no circumstance shall the investigator relocate or dispose any clinical study documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate Regulatory Authority to review any documentation relating to this clinical study, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the ICF.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the clinical study.

12.2.3. Participation Cards

If the subjects are not under 24-hour supervision of the investigator or site staff, they must be provided with a subject participation card indicating the name of the IP, the clinical study number, the investigator's name, and the site's 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

12.3. Confidentiality

The subject will receive all information as required by the EU General Data Protection Regulation, namely the identity and contact details of the controller, the contact details of the data protection officer, the clinical research purposes, the legal basis for the processing, the recipients

of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his data, and all his/her data subject's rights. All details are listed in the ICF.

All information concerning the product and the sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential and should not be disclosed by the investigator to any third party without the sponsor's prior written approval. The investigator agrees to use this information only in accomplishing the clinical study and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the clinical study, the investigator is responsible for keeping an updated Subject Identification Code List. The monitor will review this document for completeness. However, the investigator must guarantee the subject's anonymity will be maintained. Therefore, in order to ensure subject confidentiality, the Subject Identification Code List must remain at the center and no copy will be made.

12.4. Ethical Considerations

12.4.1. Independent Ethics Committee / Institutional Review Board

This clinical study can only be undertaken after IEC/IRB approval of this CSP together with all relevant documentation. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of the clinical study, at least the following documents will be submitted to the IEC/IRB, per local requirements:

- Changes to the IB
- Reports of AEs that are serious, unlisted, and associated with the IP (in compliance with IEC/IRB, per local requirements)
- CSP amendments
- ICF amendments

After the subject has completed the study, the subject will receive a financial compensation, or depending on the country, the study physician may offer the option of a course of post-study medication approved for the treatment of RA, at no cost and for a duration of up to 6 months. Subjects will be eligible for compensation in case a subject received at least 1 dose of IP and completed the study, or discontinued early for e.g. safety reasons. In case a subject withdraws from the study early compensation will be pro rata, unless the reason for withdrawal from the study is noncompliance, then no compensation will be provided. Any form of compensation and conditions for compensation will require approval by an IEC and documented in the ICF.

The IEC/IRB is responsible for continuous review of the clinical study. Where required by IEC/IRB, per local requirements, at least once a year the investigator will provide the IEC/IRB

with a progress report to allow review of the clinical study. Additional progress reports should be provided according to local legal requirements. These requests and (re-)approvals, if applicable, should be documented in writing.

12.4.2. Informed Consent

The investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, possible risks) to potential subjects according to applicable regulations prior to any clinical study-related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the clinical study at any time. They will be informed that choosing not to participate or to withdraw from the clinical study will not have an impact on the care the subject will receive for the treatment of his/her disease.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the clinical study, the subject's consent should be appropriately recorded by means of the subject's personally dated signature and by the investigator's dated signature. In case the subject is unable to read and/or write, oral consent in the presence of at least one impartial witness who was also included when the affected person was being informed, may be given. The witness may not be anyone working at the site nor a member of the investigating team. The orally given consent shall be documented in writing, dated and signed by the witness. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

If new information becomes available relevant to the subject's willingness to participate in the clinical study, the subject will be informed in a timely manner by means of an amended ICF. This amended ICF will be signed and dated by the subject (or, if applicable, by an independent witness) and the investigator to document the willingness of the subject to continue with the clinical study.

This signed and dated amended version will be filed together with the initial signed and dated ICF.

A pregnant partner, who agrees that information will be gathered about her pregnancy and the birth, will be asked to sign a specific ICF to participate in the data collection. Data about the health of the baby will be collected if the parent(s)/legal guardian(s) agree with the data collection and sign a specific ICF.

Subjects who agree to participate in the study and who have signed informed consent, will be given the option to provide additional (and optional) informed consent for the long term storage of left over samples and associated data, collected during the study, for future scientific research.

12.5. Data Quality Control/Assurance

12.5.1. Monitoring

Data quality will be assured through Risk-Based Monitoring, medical monitoring, and other relevant activities as described in the Data Management Plan or Medical Review Plan and monitoring plans available in the TMF. This clinical study will be monitored by sponsor representatives according to their current standard operating procedures.

To guarantee adequate protection of the subjects and to guarantee the quality of the data, the sponsor will ensure oversight of any clinical study-related duties and functions carried out on its behalf, including clinical study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

A risk-based Quality Management Plan (QMP) is prepared for the study that evaluates potential risks in relation to rights, safety, and well-being of the study subjects as well as the data integrity. The QMP describes and evaluates all involved stakeholder interfaces having potential critical impact on the above. Risks are considered at both the system level (e.g. standard operating procedures, computerized systems, personnel, and vendors) and study level (e.g. IP, study design, data collection, informed consent process and recording).

12.5.2. Audit and Inspection

To ensure compliance with relevant regulations, an independent quality assurance representative, regulatory authorities and/or IECs/IRBs may review this clinical study. This implies that auditors/inspectors will have the right to inspect the clinical study center(s) at any time during and/or after completion of the clinical study and will have access to the data generated during the clinical study, source documents, and subject's files. By participating in this clinical study, investigators agree to this requirement.

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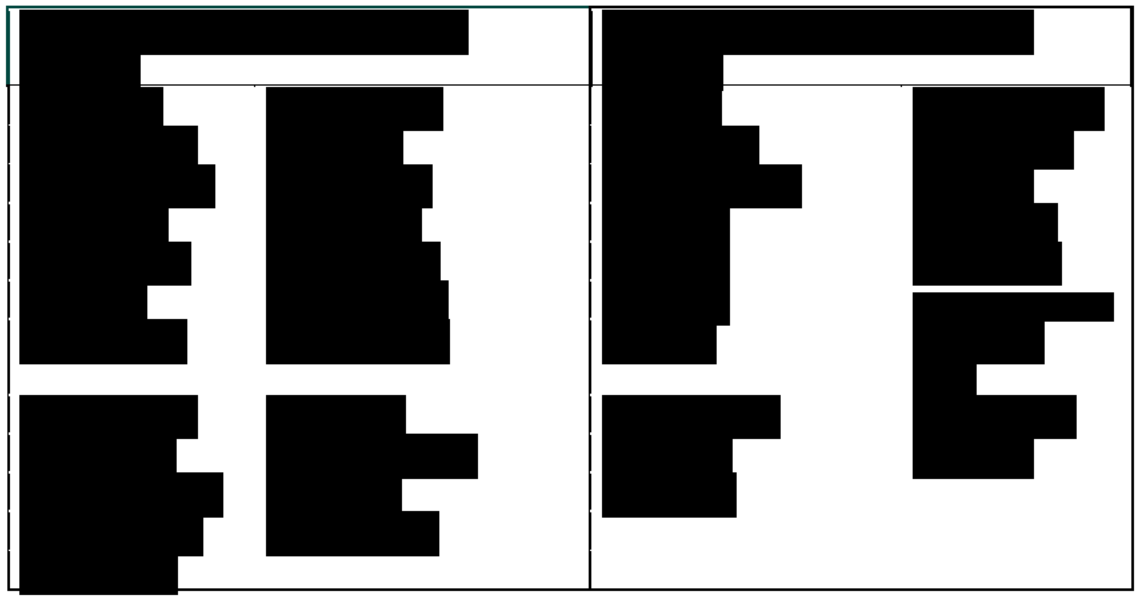
14. APPENDICES

[redacted]



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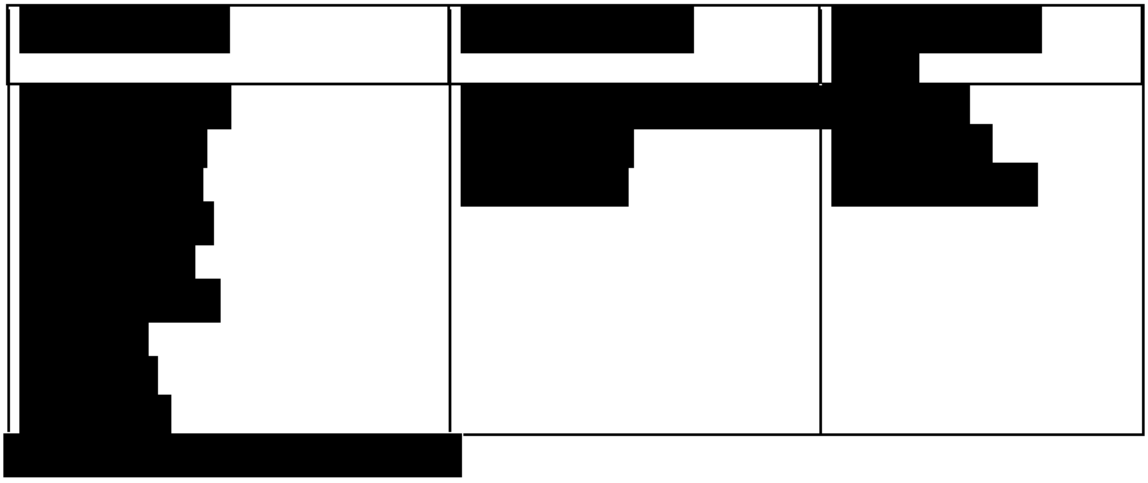

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Appendix 7: Prednisolone Conversion Table

Glucocorticoid Name	Dose Equivalent to 5 mg Prednisolone
Prednisone	5 mg
Betamethasone	0.6 mg
Cortisol (hydrocortisone)	20 mg
Cortisone	25 mg
Deflazacort	7.5 mg
Dexamethasone	0.75 mg
Methylprednisolone	4 mg
Methylprednisolone Acetate	4 mg
Methylprednisolone Sodium Succinate	4 mg
Paramethasone	2 mg
Prednisolone	5 mg
Triamcinolone	4 mg
Beclometasone Dipropionate	1.25 mg
Budesonide	1.5 mg
Hydrocortisone Sodium Succinate	20 mg

(Steriod Conversion Calculator)

Appendix 8: Algorithm for Elevated Liver Function Tests

<table>
<tr><td></td><td colspan="5">AST or ALT increase to</td></tr>
<tr><td>Value Range</td><td>≥1.5x to 3xULN</td><td>≥3x to <5xULN</td><td>≥5x to <8xULN</td><td>≥3xULN with signs of liver damage[1]</td><td>≥8xULN</td></tr>
<tr><td rowspan="2">IP Action</td><td>Continue as planned</td><td rowspan="2">Reduce or interrupt IP for at least 2 weeks

Close observation[2]</td><td rowspan="2">Interrupt IP for at least 2 weeks

Close observation[2]</td><td>Discontinue IP[2]</td><td>Discontinue IP[2]</td></tr>
<tr><td colspan="3">↙ ↘</td></tr>
<tr><td>After at least 2 weeks</td><td colspan="2">AST and ALT <3xULN</td><td colspan="3">AST or ALT ≥3xULN</td></tr>
<tr><td></td><td colspan="2">Weekly LFTs for the first 2 weeks (biweekly for the following weeks, or more frequently at investigator’s discretion)</td><td colspan="3">Discontinue IP

Report SAE and complete liver event page for any of abnormalities listed below[3]:

- AST/ALT increase ≥8xULN

- AST/ALT increase ≥3xULN with signs of liver damage[1]</td></tr>
</table>

[1] Signs of liver damage:

– total bilirubin ≥2.0xULN OR international normalized ratio >1.5, and/or

– symptoms: appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

[2] Close observation recommendations:

– Monitor 2 to 3 times per week all of the following parameters: ALT, AST, ALP, total bilirubin, eosinophils, INR. If local regulations allow, home visits can be performed if subjects cannot come to the clinical study center.

– Frequency of retesting can be reduced to once a week or less if abnormalities stabilize or the IP has been discontinued; however, monitoring might still be needed more frequently taking into consideration the standard of care and/or changes to this.

– Based upon investigator’s discretion gastroenterology or hepatology consultations, additional serology testing, imaging, and pathology assessments may be required.

– Re-query history of symptoms, prior and concurrent diseases, concomitant medication and non-prescription medicines, herbal, dietary supplements, alcohol use, recreational drug use, special diets.

– Rule out all of the following: acute viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, non-alcoholic fatty hepatitis, hypoxic/ischemic hepatitis, biliary tract disease, and cholestasis.

– Re-query exposure to environmental chemical agents.

[3] The following steps should be followed:

– The site should immediately contact the subject and require the subject to discontinue IP immediately. The subject should be asked to return to the site within a 48-hour window from awareness of the result.

– A full evaluation of various causes of hepatitis should be conducted (i.e. infectious, alcohol, medications, anatomical).

- An assessment of other concomitant medications and standard of care should be made. The investigator should consider to whether is in the best interest of the subject to stop/interrupt concomitant medications and SOC treatment.
- A detailed history including relevant information on alcohol use, recreational drug use, supplement consumption, any herbal remedies, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, occupational history, blood transfusion, history of liver or allergic disease, and any other potential causes of attributable to a liver insult should be collected.
- A detailed assessment of the subject's clinical condition and repeat laboratory tests for LFT, including albumin, creatine kinase, total bilirubin (direct and indirect), GGT, INR, and ALP should be done.
- Further testing for Hepatitis A, B, and C, and for autoimmune hepatitis should be done. Other causes of viral hepatitis (cytomegalovirus or Epstein-Barr virus etc) should be excluded. Liver imaging should be considered.
- Referral to a hepatologist or gastroenterologist should be requested.
- All these cases should be reported as SAEs.

Appendix 9: 66/68 Joint Count

Joints Assessed (left and right) for Swelling (66 Joints) and/or Tenderness (68 joints)

Temporomandibular
Sternoclavicular
Acromioclavicular
Shoulder
Elbow
Wrist
Metacarpophalangeal
- First
- Second
- Third
- Fourth
- Fifth

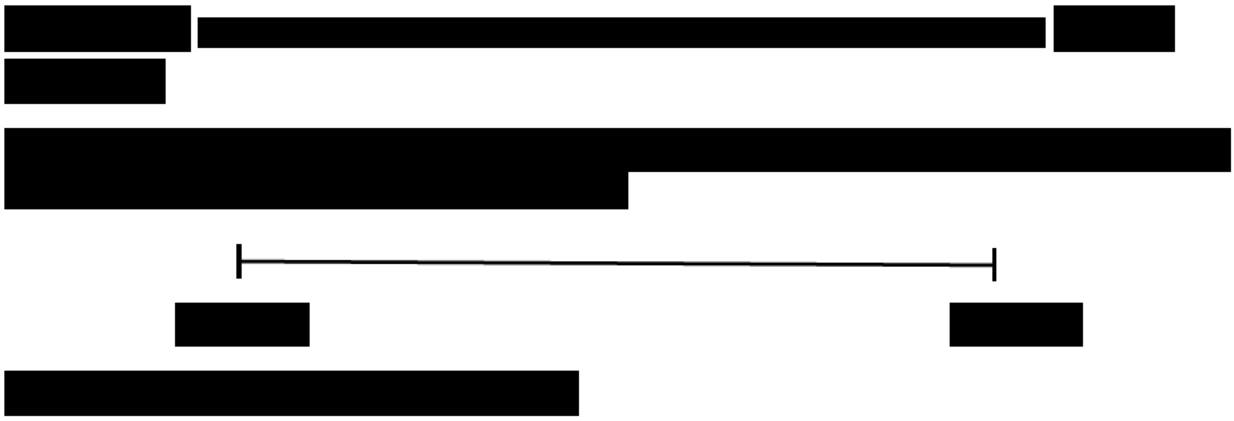
Proximal interphalangeal
- First
- Second
- Third
- Fourth
- Fifth

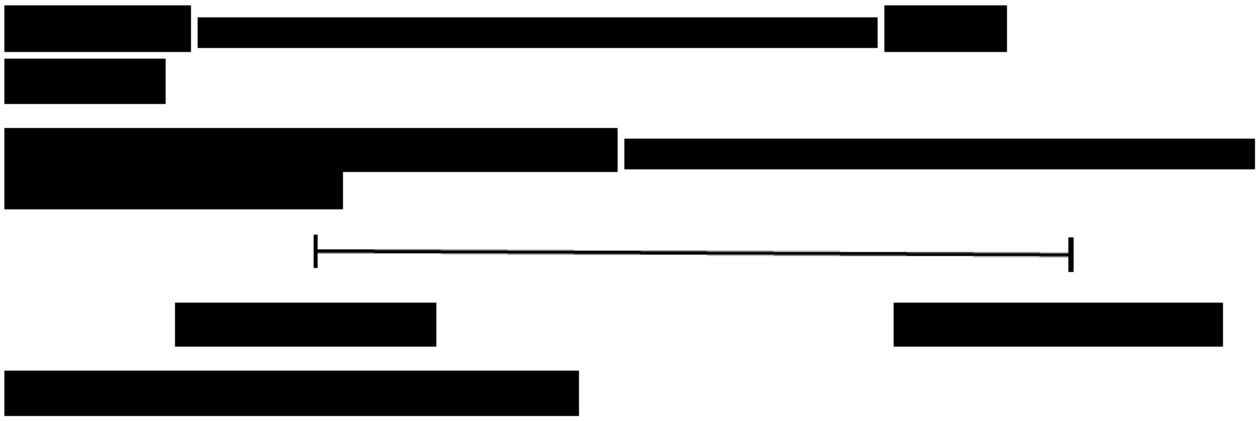
Distal interphalangeal
- Second
- Third
- Fourth
- Fifth

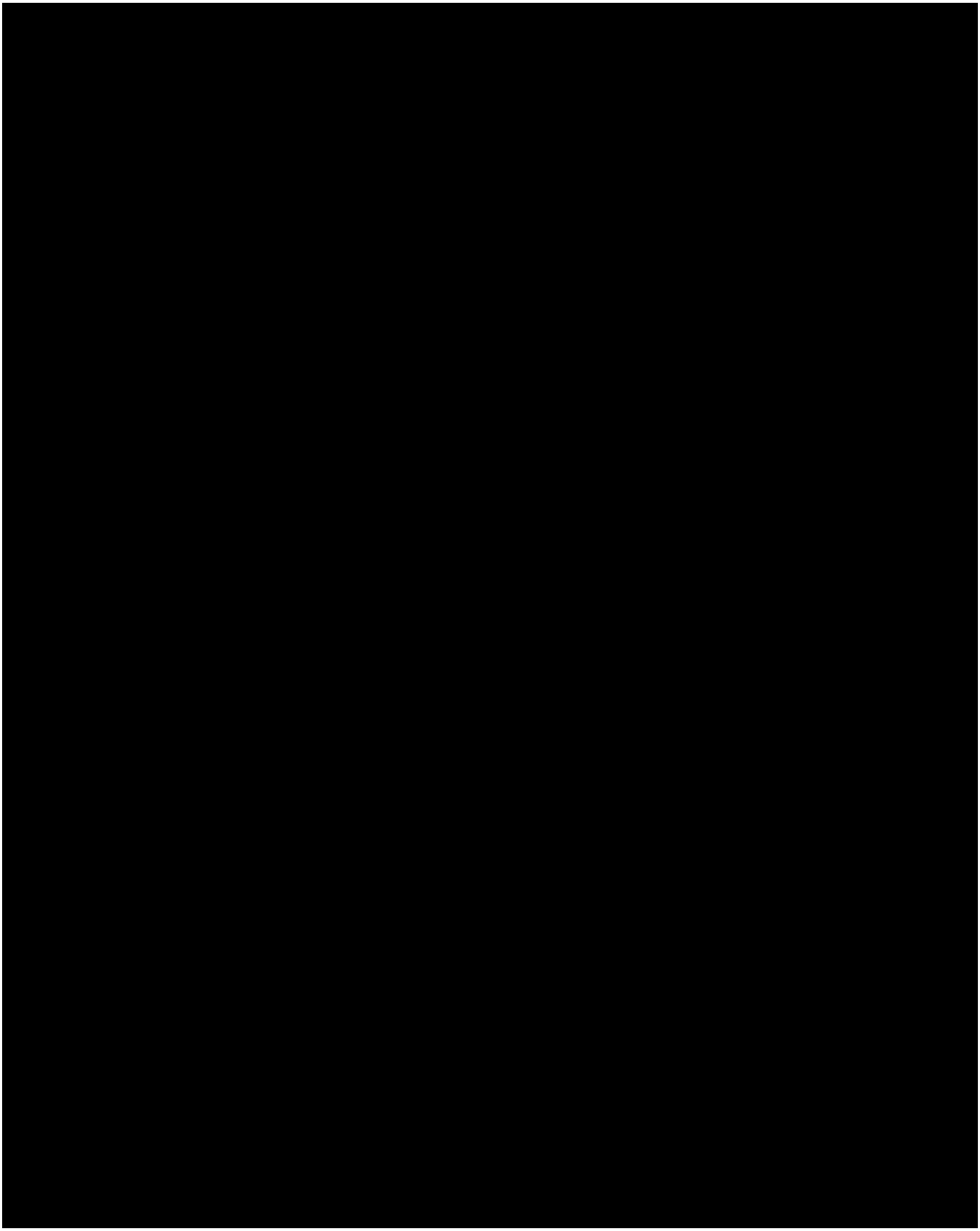
Hip #
Knee
Ankle
Tarsus
Metatarsophalangeal
- First
- Second
- Third
- Fourth
- Fifth

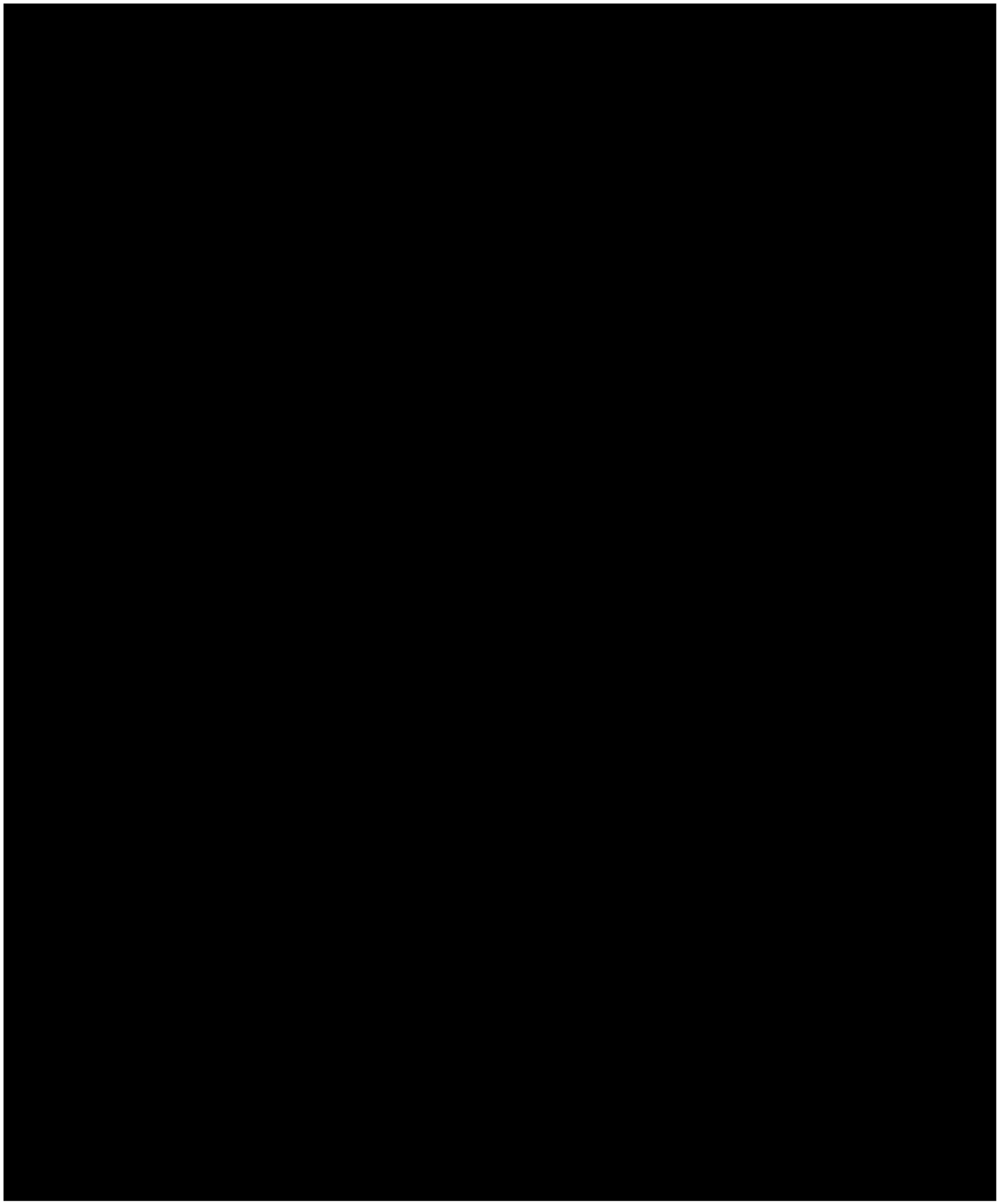
Proximal interphalangeal (toe)
- First
- Second
- Third
- Fourth
- Fifth

#Assessed for tenderness only









SIGNATURE PAGE – SPONSOR

Study Title:	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy and pharmacokinetics of GLPG3970, administered orally for 6 weeks in adult subjects with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate	
CSP Version:	1.0	Date:

This clinical study protocol has been reviewed and approved by the sponsor to ensure compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Scientific Leader	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title:	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, efficacy and pharmacokinetics of GLPG3970, administered orally for 6 weeks in adult subjects with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate
CSP Version:	1.0 Date:

I, the undersigned, have read this clinical study protocol and will conduct the study as described in compliance with the clinical study protocol, in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Investigator Name	Signature	Date

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Approval	[redacted]ment 29-May-2020 12:43:46 GMT+0000

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