A 12-week, phase II, multicentre, randomised, double blind, efficacy and safety study comparing CPL409116 to placebo, in combination with methotrexate in participants with active rheumatoid arthritis who have an inadequate response to methotrexate

03JAK2021

Statistical Analysis Plan

Protocol version number and date:	Version 3.0, 20 December 2022
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Summary of Changes

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Signatures

Author: [redacted]

Date, Signature

Author: [redacted]

Date, Signature

Sponsor: [redacted]

Date, Signature

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List of abbreviations

ACPA	Anti-citrullinated protein autoantibodies
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AR(1)	Autoregressive
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical Classification System
AUC	Area under the curve
$AUC_{(0-6h)}$	Area under plasma concentration-time curve from zero to 6 h after dosing
$AUC_{(0-t)}$	The area under plasma concentration-time curve, from time point zero to the last measurable analyte concentration in plasma
$AUC_{(0-inf)}$	Area under plasma concentration-time curve from zero to infinity
AUC_{tau}	Area under plasma concentration-time curve from dosing time to dosing time plus tau (12 h)
BID	bis in die, twice a day
BMI	Body mass index
BP	Blood pressure
BT	Body temperature
CDASH	Clinical Data Acquisition Standards Harmonization
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Apparent clearance
CRO	Clinical Research Organization
CRP	C-reactive protein
CS	Compound symmetry
CSR	Clinical Study Report
C_{av}	Average concentration in the dosing interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
C_{trough}	Concentration immediately prior to dosing
DAS	Disease Activity Score
DBP	Diastolic blood pressure
DMARDS	Disease-Modifying and Anti-Rheumatic Drugs
ECG	Electrocardiogram

(e)CRF	(electronic) Case Report Form - may be a paper or electronic representation of the data collection tool
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOS	End of study
ESR	Erythrocyte Sedimentation Rate
EULAR	The European Alliance of Associations for Rheumatology
EW	Early withdrawal
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FAS	Full analysis set
FSH	Follicle stimulating hormone
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HBV DNA	hepatitis B DNA
HCVAb	hepatitis C antibody
HCV RNA	hepatitis C RNA
HDL	High- density lipoprotein
HIV	Human immunodeficiency virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Committee of Harmonization
IMP	Investigational Medicinal Product
IP	investigational product
IQR	Inter quantile range
ITT	Intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	Interactive Web Response System
K_{el}	Termin elimination rate constant
LDL	low-density lipoprotein
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LS mean	Least squares mean
MCS	Mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measure
MRT	Mean Residence Time

MTX	Methotrexate
M3	M3 metabolite of CPL409116
NA	Not Available
NRI	Non-responder imputation
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
PAAP	Patient's Assessment of Arthritis Pain
PCS	Physical Component Score
PD	Pharmacodynamics
PhGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetic / Pharmacokinetics
PP	Per protocol set
PS	Pharmacokinetic Set
PSPC	Pharmacokinetic Set for parameter calculation
PT	Preferred term
PtGA	Patient Global Assessment of Arthritis
QFT-G	QuantiFERON-TB GOLD
QQ	quantile-quantile
QRS	QRS complex interval consisting of a Q-, R- and S-wave
QTc	QT interval corrected for heart rate using Fridericia's correction
RA	Rheumatoid arthritis
RBC	red blood cell count
RR	Respiratory Rate
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	36-Item Short Form Survey Instrument
SJC	Swollen Joint Count
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety set
SmPC	Summary of Product Characteristic
$t_{1/2}$	Apparent terminal elimination half-life
TJC	Tender Joint Count
t_{lag}	Time to measurable (non-zero) plasma concentration
t_{max}	Time corresponding to occurrence of C_{max}
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
ULN	upper limit of normal

VAS	visual analog scale
Vz/F	Apparent volume of distribution during terminal phase
WBC	white blood cell count
WONCB	women of non-childbearing potential

1. Introduction

This statistical plan reflects study protocol 03JAK2021 version 3.0, dated 20 December 2022. It follows the principles of the Guidelines ICH Topic E3 and ICH Topic E9.

All aspects of the statistical analysis shall be covered by this document. It provides a technical and detailed description of handling the collected data and statistical methods deployed.

1.1. SOPs to be followed

The statistical analysis will be carried out according to Biostat SOPs. The statistical report will be written according to the ICH Guidelines.

2. Overview of the protocol

2.1. Objectives of the study

2.1.1. Primary objectives

Efficacy:

To determine the efficacy of CPL409116 at 12 weeks, in subjects with active RA who have had an inadequate response to methotrexate (MTX).

2.1.2. Secondary objectives

Efficacy:

- To determine the effect of CPL409116 at 3 different doses, compared to placebo in subjects with rheumatoid arthritis.
- To assess dose-response and exposure- response relationship for CPL409116.

Safety:

- To evaluate safety and tolerability of CPL409116 administered at doses: 60 mg, 120 mg or 240 mg twice a day for 12 weeks in subjects with RA.

Pharmacokinetics:

- To evaluate pharmacokinetic (PK) parameters for CPL409116 and metabolite M3 in patients with RA.

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2.1. Endpoints

2.1.1. Primary study endpoints

Primary endpoint is to be:

- Change from Baseline in Disease Activity Score (DAS)28- C Reactive protein (CRP) at Week 12.

2.1.2. Secondary endpoints

Clinical Efficacy:

- Proportion of subjects with DAS28-CRP remission at Weeks 4; 8; 12 and 16.
- American College of Rheumatology (ACR)20, ACR 50, ACR 70, and ACR 90 responder rates (Weeks 4, 8 and 12).
- Change from Baseline in the Tender/Painful and Swollen Joint Count (Weeks 4, 8 and 12).
- Change from Baseline in the Physician's Global Assessment (PhGA) of Arthritis (Weeks 4, 8 and 12).

Patient Reported Outcome:

- Change from baseline in the Patient's Assessment of Arthritis Pain (PAAP) VAS and Patient Global Assessment of Arthritis (PtGA, VAS) at Week 4, 8, and 12.
- Change from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 4, 8, and 12.
- Change from baseline in the SF-36 RAND 8 Domain scores and Physical Component Score (PCS) and Mental component score (MCS) at Week 12.
- Change from baseline in the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) total score at Week 12.

Safety:

Safety and tolerability of CPL409116: vital signs (blood pressure (BP), pulse and temperature), laboratory tests, Adverse Events (AEs) and Serious Adverse Events (SAEs), 12-lead electrocardiogram (ECG):

- Incidence and severity of adverse events, serious adverse events, and withdrawals due to adverse events (Baseline through Week 16).
- Incidence of abnormality in clinical chemistry parameters (Baseline through Week 16).
- Incidence of abnormality in haematological parameters (Baseline through Week 16).
- Change from baseline in blood pressure measurement (Baseline through Week 16).
- Change from baseline in pulse rate measurement (Baseline through Week 16).
- Change from baseline in temperature measurement (Baseline through Week 16).
- Incidences of targeted medical adverse events (Baseline through Week 16).

Pharmacokinetics:

- CPL409116 and metabolite M3 pharmacokinetic variables: $AUC_{(0\text{-}6h)}$, C_{max}, T_{max}, $T_{1/2}$ (if possible) and K_{el} (if possible) determined on Day 1, 8, 57 and 85.
- CPL409116 pharmacokinetic variables: C_{0h}, $C_{2.5h}$ determined on Day 29.

2.2. Study design

This is a 12-week, phase II, multicentre, randomised, double blind, efficacy and safety study of CPL409116 in participants with active rheumatoid arthritis who are taking methotrexate but have an inadequate response to this drug.

Approximately 100 male and female subjects are to be enrolled in the study. Eligible subjects are to be randomized into one of the 4 treatment arms determined in points below:

- 25 are to be randomized to the treatment arm with CPL409116 at a dose of 60 mg BID;
- 25 are to be randomized to the treatment arm with CPL409116 at a dose of 120 mg BID;
- 25 to the treatment arm with CPL409116 at a dose of 240 mg BID;
- 25 to the treatment arm with placebo.

Randomisation ratio is to be: 1:1:1:1. This will be the age-stratified randomisation. In all treatment arms investigated product/ placebo is to be administered orally for 12 weeks in a blinded fashion. In order to maintain the blind and minimize bias, all subjects will receive the same number and types of tablets each day of treatment.

The study consists of 3 phases:

- A Screening phase of up to 4 weeks,
- A double-blind treatment phase (Day 1 to Day 85/86; 12 weeks) with two doses of IMP administration per day (except Day 85 when patients are to ingest only one dose of IMP in the morning and except Day 86 without administration of CPL409116, when the last sample of blood will be collected for PK analysis in the morning),
- A 4 weeks post-treatment follow-up phase up to Week 16 (Day 113). Patients are to come to a study centre two times after the last dose of IMP. According to the schedule assessment in the follow-up period are planned two ambulatory visits and phone calls from clinical centres: Week 14 and 16 (Day 99 and 113 respectively)- an ambulatory visit; Week 13 and 15 (Day 92 and 106 respectively)- phone call from a clinical centre. The end of the study is planned at Week 16 (Day 113).

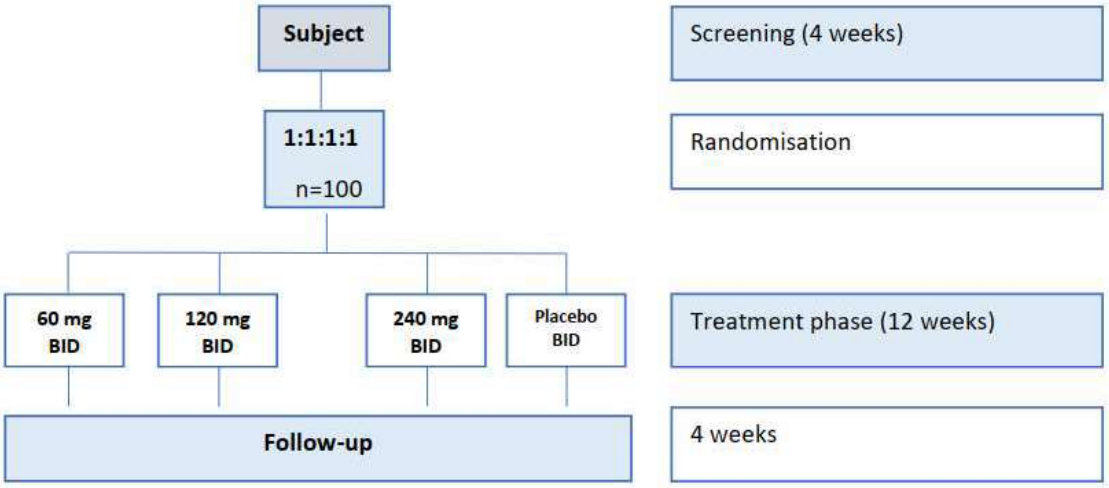

Figure 1. Study design

In the **Screening Period**, patients undergo screening assessments from Day -28 to Day 0. Rolling admission is employed in this study. Patients that fulfil all the inclusion criteria and none of the exclusion criteria will be considered eligible for this study. Subjects must complete all screening procedures and assessments and have test results available prior to the Baseline visit (Visit 2).

Randomisation will take place at the end of the Screening period when it is confirmed by an Investigator that a participant fulfilled all inclusion criteria and none of exclusion criteria available at the time of randomisation (pre-final confirmation). Patients will be randomised at the end of the screening period (1-2 days before Day1/ Baseline) in order to generate the randomisation code which is necessary to prepare appropriate number of IMP/ placebo for a patient. Pre- final conformation will take place after the negative result of COVID-19 test is received. The rest of inclusion and exclusion criteria unavailable at Screening will be verified on Day1/ Baseline (final conformation). The final conformation will take place before the first dose of IMP/placebo administration on Day1/ Baseline.

After randomization and during the **Treatment Period**, patients are to be dosed with 60, 120 or 240 mg CPL409116 administered twice a day or matching placebo administered twice a day for 85 consecutive days (Day 1 to Day 85; the last dose of IMP is taken by subject on Day 85 as the morning dose). Study visits are calculated from Visit 2 Baseline/Day 1/Week 0. All visits should take place as close to the scheduled visit day as possible. In case of unpredictable events (participant hospitalization, the site closure, etc.) which can have an impact on scheduled visit a new visit day should be scheduled or rescheduled as close to the original visit date as possible.

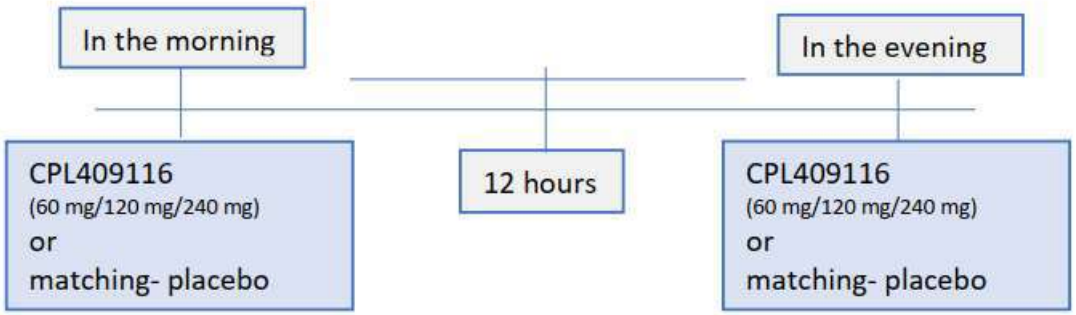

Figure 2. Dosing sequence scheme during the day

During the treatment period apart from the IMP administration patients are to administer methotrexate (MTX) as a continuation of the background RA therapy. MTX must be administered for at least 12 weeks prior to Screening, and with no change in dosage and route of administration for at least 8 weeks prior to Day 1/ Baseline. The MTX dosage at Baseline (ranged from 15-25 mg/week, which is typical of current Polish practice) and route of administration is to remain stable during the study. A lower dose of ≥10 mg/week is acceptable if reduced for reasons of side effects or intolerance to MTX, e.g. nausea/vomiting, hepatic or hematologic toxicity (there must be clear documentation in the medical record).

All patients will undergo PK sampling during the Treatment Period. Timepoints are indicated on the basis of PK results from PART B of the study 01JAK2020. Blood samples collection for PK analysis will take place on Day 1/ Baseline; 8; 29; 57 and 85/86. Blood samples for PK analysis are to be collected on the following time points: on Days 1, 8, and 57 at timepoints: pre-dose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, and 6.0h after CPL409116 administration in the morning; and on Day 29 at timepoints: pre-dose (0.0) and 2.5h after CPL409116 administration in the morning. On Day 85 PK blood sample collection is to be carried out in 13 timepoints, as follows: pre-dose (0.0) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, and 24h (Day 86) after CPL409116 administration in the morning.

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Investigational product tablets will be administered to the subject in the clinic on the morning of clinic visits and all other dosing will be performed by the subject outside the clinic, at home. Additionally, apart from ambulatory visits which take place on Day 1/ Baseline; 8; 29; 57 and 85, on Day 43 (Week 6) and on Day 71 (Week 10) phone call to patients will be made to monitor potential adverse events and compliance check.

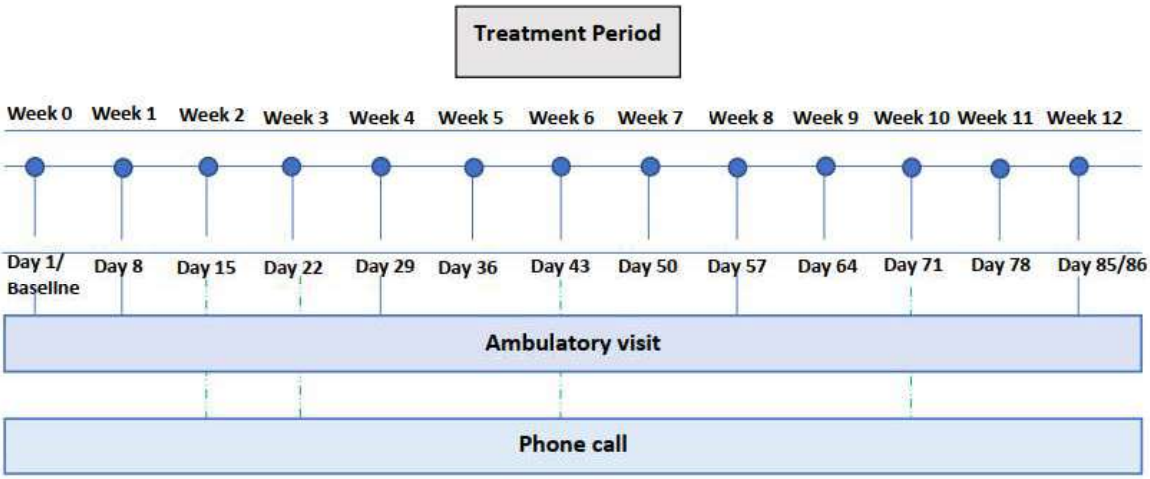


Figure 3. Scheme of 12-week treatment period

Between ambulatory visits subjects are to administer investigational medicinal product outside the clinic, at home. During the Day1/ Baseline subject diary and appropriate number of tablets with active substance or placebo will be dispensed in a clinical site. Subjects are to be obligated to complete the diary every time after investigational product administration (in the morning and in the evening). The diary is to be verified during ambulatory visits on the following Days: 8, 29, 57 and 85 to IMP accountability and compliance check. At every outpatient visit appropriate number of CPL409116/placebo tablets and a new part of the Patient's diary will be dispensed whereas the previous part of diary (completed) is to be attached to the documentation of the study. The last part of the Patient's diary is to be dispensed on Day 57 (Week 8) and collected on Day 85 (Week 12). If required patients will be retrained during ambulatory visits. Subjects are to be obligated to hand empty aluminum blisters back to a clinical unit.

Within the **Follow-up Period** patients are to come to the study centre two times after the last dose of IMP: Week 14 and Week 16 (Day 99 and Day 113 respectively). On Day 92 and on Day 106 the phone call from the study unit will be made.

Patients that withdraw or are withdrawn from the study will attend an early termination visit at the study unit and 2 safety Follow-up visits after the last dose of IMP.

2.2.1. Inclusion-Exclusion Criteria and General Study Population

Male and female patients with a diagnosis of with moderate-severe active rheumatoid arthritis (RA) who have had an inadequate response to methotrexate (MTX).

Subjects must complete all screening procedures and assessments and have test results available prior to the baseline visit (Visit 2). If patient's status after Screening changes at Baseline (Day 1) and the patient no longer meets all eligibility criteria, the patient should be excluded from participation in the study (such patient is to be considered as a screen failure).

Inclusion Criteria

Subjects eligible for inclusion in this study must fulfil all of the following criteria:

1) Age ≥18 and ≤75 years at the time of signing informed consent.
2) Meets ACR/EULAR 2010 RA Classification Criteria with a duration of RA disease of ≥6 months at time of screening and participant not diagnosed before 16 years of age.
3) Must have active disease at both screening and baseline, as defined by having all three listed below:
    a) ≥ 6/68 tender/painful joints (TJC),
    b) ≥ 6/66 swollen joints (SJC).
    c) DAS28> 3.2

NOTE: If surgical treatment of a joint has been performed, that joint cannot be counted in the TJC or SJC for enrolment purposes.

4) Must have a C-reactive protein (CRP) measurement ≥7 mg/L at screening.

NOTE: If patient's CRP level is below 7 mg/L on Screening visit, it is possible to perform CRP measurement once again within 28 days of Screening period, provided at least 14 days since initial CRP measurement and prior to Day -5 before Baseline.

5) Must meet Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.
6) Must have inadequate response, despite currently taking Methotrexate (MTX): weekly 15-25 mg oral or injected (subcutaneous or intramuscular) for at least 12 weeks prior to Screening, and with no change in dosage and route of administration for at least 8 weeks prior to Day 1/ baseline. A lower dose of ≥10 mg/week is acceptable if reduced for reasons of side effects or intolerance to MTX, e.g nausea/vomiting, hepatic or hematologic toxicity (there must be clear documentation in the medical record).
7) If using oral GCS must be on stable dose (equivalent to ≤10mg/day of prednisone) for at least 4 weeks prior to Day 1/ baseline.
8) If using NSAIDs must be on stable dose for at least 4 weeks prior to Day 1/ baseline.
9) A woman must be either:
    a) Not of childbearing potential:
        - postmenopausal: >45 years of age with spontaneous amenorrhea for at least 12 months. In addition, in women under the age of 60 years postmenopausal status must be confirmed with FSH level ≥ 40 IU/L at screening, without using hormone replacement therapy (women treated with hormone replacement therapy require a wash-out period in order to obtain physiologic FSH level; the duration of the wash-out depends on the type of hormone replacement therapy and the Investigators should use their judgment in determining the wash-out period);
        - permanently sterile (hysterectomy, bilateral salpingectomy; bilateral oophorectomy); or otherwise be incapable of pregnancy.

NOTE: premenopausal women who have had a bilateral tubal ligation/occlusion are considered capable of becoming pregnant.

    b) Of childbearing potential and using a double contraception including a barrier method (condom or occlusive cap) and a highly effective method of birth control (listed below):

NOTE: highly effective methods of contraception are defined as:

- established use (i.e. at least 8 weeks prior to Day 1) of combined (estrogen and progesterone) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal, injectable) or progesterone-only hormone contraception associated with inhibition of ovulation (oral, injectable);
- intrauterine device (IUD) or intrauterine hormone-releasing system (IUS);
- bilateral tubal occlusion/ligation;
- vasectomized partner (vasectomized partner should be the sole partner for that subject and the absence of sperm should be confirmed).

NOTE: sexual abstinence, defined as refraining from heterosexual intercourse throughout the study and for 12 weeks after the last IMP dose, is acceptable as a sole contraception method when this is in line with the preferred and usual lifestyle of the subject.

10) Participant (a man) who is sexually active with a woman of childbearing potential must agree to use a double contraception including a barrier method (male condom) and a highly effective method of contraception (highly effective method of contraception are listed above) during the study and 12 weeks after the last dose of CPL409116/ placebo administration.

NOTE: Male subjects are responsible for informing his partner(s) of the risk of becoming pregnant and for reporting any pregnancy to the study doctor.

NOTE: Participants (males and females) are furthermore willing to use contraception methods for 12 weeks after the last dose of CPL409116/ placebo administration. It is crucial to maintain appropriate methods of contraception if it is planned to continue methotrexate administration after the end of the study.

11) A woman of childbearing potential must have a negative blood pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening and negative urine pregnancy test on Day1/ baseline.
12) Informed Consent Form signed and dated prior to Screening evaluations.
13) Ability and willingness to comply with the requirements of the study Protocol.
14) Negative result of the COVID-19 RT-PCR test (real-time reverse transcription polymerase chain reaction) for the qualitative detection of nucleic acid coming from SARS- CoV-2 before inclusion to the study (Screening- 72 h before Day1/ baseline).

Exclusion Criteria

Subjects eligible for inclusion in this study must **not** fulfil any of the following criteria:

1) Has had a serious infection (e.g. sepsis, pneumonia, pyelonephritis or any other serious infection as per Investigator's judgement), or has been hospitalized or received intravenous antibiotics for an infection within 3 months prior to Day 1/ baseline.
2) Any active infection including localized infections within 2 weeks prior to baseline.

3) History of opportunistic or recurrent (3 or more of the same infection requiring anti-infective treatment in any rolling 12-month period) infection.
4) History of chronic infections requiring anti-infective treatment within 6 months prior to Screening.
5) Subjects with a high risk of infection in the Investigator's opinion (e.g. subjects with leg ulcers, indwelling urinary catheter).
6) History of infected joint prosthesis or other implanted device with the retention of prosthesis or device in situ.
7) Symptomatic herpes zoster within 3 months prior to Screening
8) History of disseminated herpes simplex infection or disseminated/complicated herpes zoster.
9) Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
10) Known infection with human immunodeficiency virus (HIV) or positive test at Screening.
11) Presence of any of the following laboratory abnormalities at Screening:

    a) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels 1.5 x the upper limit of normal (ULN);
    b) Absolute neutrophil count of <1.5 x 109/L (<1500/mm3);
    c) Absolute lymphocyte count of <0.75 x 109/L (<750/mm3);
    d) Absolute white blood cell (WBC) count of < 3.0 x 109 /L (<3000/mm3);
    e) Hemoglobin <9.0 g/dL (90 g/L);
    f) Thrombocytopenia, as defined by a platelet count <100 x 109/L (< 100 000/mm3) at Screening;
    g) Total bilirubin ≥1,5× the upper limit of normal (ULN).

12) Current or history of clinically significant (per Investigator's judgment) liver or biliary disease or significantly abnormal liver function test at screening (ALT or AST level ≥ 1.5 x ULN and/or total bilirubin ≥1,5× the upper limit of normal (ULN).
13) Current acute or chronic HCV and/or HBV infection:
    a) subjects who are seropositive for antibodies to hepatitis C virus (at Screening) may be allowed to participate in the study provided they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to Screening, and have a third negative HCV RNA test result at Screening.
    b) HBV serology:

        - a positive result for HBsAg will be exclusionary;
        - a positive result for anti-HBc antibodies in subjects negative for HBsAg requires HBV DNA testing. A positive test result for HBV DNA will be exclusionary;
        - for subjects who are negative for HBsAg and anti-HBc antibodies and has had a HBV vaccination a positive test result for anti-HBs antibodies is expected – such subjects may be enrolled without HBV DNA testing. In non-vaccinated patients positive for anti-HBs antibodies HBV DNA testing is required;
        - a positive result for HBV DNA will be exclusionary.

NOTE: enrolled subjects positive for anti-HBc antibodies and/or anti-HBs antibodies (except for vaccinated subjects negative for anti-HBc antibodies and positive for anti-HBs antibodies) will have repeated HBV DNA testing at week 6 (or early termination visit) and last follow-up visit. A positive result for HBV DNA testing in these subjects will require immediate interruption of study drug and a hepatologist consultation.

14) Current or history of clinically significant renal disease (per investigation judgment) or eGFR<60mL/min/1.73m2.
15) Breast cancer or other malignancy (including lymphoma, leukemia) within the past 5 years except for cervical carcinoma in situ that has been completely resected with no evidence of recurrence or metastatic disease for at least 12 months or cured basal cell carcinoma with no evidence of recurrence for at least 12 months.
16) History of major organ transplant (e.g. kidney, heart, liver, lung) or hematopoietic stem cell/bone marrow transplant.
17) History of lymphoproliferative disease or signs/ symptoms suggestive of possible lymphoproliferative disease, including splenomegaly of lymphadenopathy.
18) History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.
19) History or presence of other significant concomitant illness that, according to the Investigator's judgment, would place the participant at unacceptable risk when taking investigational product or could interfere with the interpretation of data.
20) History of other (than RA) chronic inflammatory arthritis or systemic autoimmune disorder other than Sjögren's syndrome secondary to RA, that may confound the evaluation of the effect of the study intervention such as mixed connective tissue disease, psoriatic arthritis, juvenile chronic arthritis, spondyloarthritis, Felty's Syndrome, systemic lupus erythematosus, scleroderma, Crohn's disease, ulcerative colitis, or vasculitis.
21) Presence of fibromyalgia that, in the Investigator's opinion, would make it difficult to appropriately assess RA activity for the purposes of this study.
22) Undergone any major surgery within 8 weeks prior to study entry or will require major surgery during the study that, in the opinion of the Investigator would pose an unacceptable risk to the participant.
23) Current or previous active Mycobacterium tuberculosis (TB) regardless of treatment.
24) Evidence of latent TB (as documented by a positive QuantiFERON-TB test at Screening, no findings on medical history or clinical examination consistent with active TB, and a normal chest radiograph).
25) Previous household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB.
26) Clinically significant multiple or severe drug allergies or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
27) Inherited or acquired thrombophilia and/ or current or history of thromboembolic events/ disease.
28) Screening 12-lead ECG that demonstrates relevant abnormalities that, in the opinion of the Investigator, are clinically significant and indicate an unacceptable risk for the subject's participation in the study (eg, QTc >450 msec or a QRS interval >120 msec). If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS values should be used to determine the subject's eligibility.
29) Pregnancy or breast- feeding.

NOTE: Women of childbearing potential must have a negative pregnancy test at Screening, at randomization and at scheduled visits throughout the study.

30) Narcotic and alcohol addiction or abuse (more than 14 alcohol units per week: one unit = 150 mL wine, 360 mL beer, 45 mL 40 % spirits) (UK guidelines).

31) Positive drug screen or alcohol breath tests.
32) Blood donation within the last month before Day1/ baseline.
33) Current therapy with any disease-modifying antirheumatic drug (DMARD) other than MTX. AllDMARDs (except for MTX) must be ceased before Day 1/ baseline, as follows:

- 1 month before: etanercept, sulfasalazine, chloroquine/ hydroksychloroquine;
- 3 months before: leflunomide (4 weeks in case of cholestyramine washout);
- 3 months before: adalimumab, golimumab, infliksimab, certolizumab, tocilizumab, gold, cyclosporine, penicillamine, azathioprine.

NOTE: For biological agent, previous use of one (and only one) treatment listed above (tocilizumab or TNF-alpha inhibitor) is allowed, if administered for less than 3 months or ceased because of other than lack of effectiveness causes.

34) Previous use of:
    a) Cyclophosphamide
    b) Tacrolimus
35) Previous use of JAK inhibitors.
36) Previous use of biologic agent other than tocilizumab or TNF-alpha inhibitor except for biologic agents that were considered as DMARDS and used as an investigational medicinal product within a clinical trial if a 30 days or 5 half-lives (whichever is longer) washout period was applied.
37) Vaccinated with a live vaccine (i.e. containing live or attenuated pathogens) within 3 months before Day 1/ baseline or necessity to vaccinate during the clinical trial.

NOTE: Investigators should ensure that all study enrolment criteria have been met at Screening and on Day 1. If a patient status after Screening changes at baseline (Day 1) such that the study patient no longer meets all eligibility criteria, then the patient should be excluded from participation in the study (such patient is to be considered as screen failure). History or presence of any other medical or psychiatric condition, or laboratory abnormality that, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation or may interfere with the study results should be considered as an exclusion criterion.

2.2.2. Randomization and blinding

Both subjects and investigators will be blinded to treatment assignment using Interactive Web Response System (IWRS) system. A computer generated randomization schedule was prepared by Dicella Ltd. and subsequently uploaded to BIOSTAT Sp. z o. o. Electronic Data Capture system (EDC). The randomization is balanced by using randomly permuted blocks and stratified by age (with 57 years used as a cut-off). Investigator are able to break the blind for a given subject, in case of emergency, using tool provided within eCRF. Bioanalytical laboratory will be blinded until complete plasma CPL409116 and M3 metabolite concentrations table is provided to Clinical Department of Celon Pharma S.A.

2.2.3. Study assessments

Details on procedures and timing of assessments are presented in the table below.

Table 1. Study schedule and assessment

Protocol activity	Screening	Treatment Period							Follow UP	End of Study	Early Withdrawal
Visit No	1	2	3	4	5	6	7	8	9	10	
Study Day/ Week	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit						N/A	±2 Days based on Week 0/Day 1 visit		
Informed consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics and RA history	X										
Prior RA medications [(c)]	X										
Medical history and prior non RA medication history	X										
History of Alcohol and Drug Abuse	X										
Height & Weight	X										
Vital Signs (Pulse, blood pressure), temperature [(d)]	X	X	X	X		X		X	X	X	X
Complete Physical Examination [(e)]	X	X							X	X	X

Protocol activity	Screening	Treatment Period							Follow UP	End of Study	Early Withdrawal
Visit No	1	2	3	4	5	6	7	8	9	10	
Study Day/ Week	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit						N/A	±2 Days based on Week 0/Day 1 visit		
Targeted Physical Examination [f]			X			X		X			
ECG (12 lead) [g]	X	X	X					X		X	X
Chest X-ray [h]	X										
Laboratory tests [i]								7			
Blood Chemistry, Hematology [j]	X	X	X	X		X		X	X	X	X
Coagulology [j]	X	X	X	X		X		X	X	X	X
Rheumatoid Factor (RF) [k]	X	X	X	X		X		X	X	X	X
C-Reactive Protein (CRP) [l]	X	X	X	X		X		X	X	X	X
Erythrocyte Sedimentation Rate (ESR) [m]	X	X	X	X		X		X	X	X	X
Anti CCP Antibodies (ACPA) [n]	X	X		X		X		X		X	X
Lipid Profile [o]	X	X	X	X		X		X	X	X	X
Blood Pregnancy test [p]	X										

Protocol activity	Screening	Treatment Period							Follow UP		End of Study	Early Withdrawal
Visit No	1	2	3	4	5	6	7	8	9		10	
Study Day/ Week	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14		Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99		Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit						N/A	±2 Days based on Week 0/Day 1 visit			
Serum FSH (WONCBP only) [q]	X											
Urinalysis with microscopy [r]	X	X	X	X		X		X	X		X	X
Urine Pregnancy test [s]		X	X	X		X		X	X		X	X
Contraception check [t]	X	X	X	X		X		X	X		X	X
HBsAg, HBcAb, HBsAb; HBV DNA; HCVAb and HCV RNA; [u]	X				(X)							(X)
HIV testing [v]	X											
Tuberculosis test [w] QuantiFERON test	X											
SARS-CoV-2 (PCR testing) [x]	X											
Toxicology (urine drug test; alcohol breath testing) [y]	X	X	X	X		X		X	X		X	X
Safety assessment												
Adverse events monitoring [z]	X	X	X	X	X	X	X	X	X		X	X

Protocol activity	Screening	Treatment Period							Follow UP	End of Study	Early Withdrawal
Visit No	1	2	3	4	5	6	7	8	9	10	
Study Day/ Week	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit						N/A	±2 Days based on Week 0/Day 1 visit		
[redacted]											
Special laboratory studies/ Blood collection for PK analysis (aa)		X	X	X		X		X →			
[redacted]											
Efficacy assessments (cc)											
Tender/Painful Joint Count (68)	X	X		X		X		X		X	X
Swollen Joint Count (66)	X	X		X		X		X		X	X
Physician Global Assessment of Arthritis (PhGA)		X		X		X		X		X	X
Patient Assessment of Arthritis Pain (PAAP) VAS		X		X		X		X		X	X

Protocol activity	Screening	Treatment Period							Follow UP	End of Study	Early Withdrawal
Visit No	1	2	3	4	5	6	7	8	9	10	
Study Day/ Week	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit						N/A	±2 Days based on Week 0/Day 1 visit		
Patient Global Assessment (PtGA) of Arthritis VAS		X		X		X		X		X	X
HAQ-DI		X		X		X		X		X	X
FACIT-Fatigue		X						X		X	X
DAS28-CRP assessment	X	X		X		X		X		X	X
SF-36 RAND		X						X		X	X
Administration of CPL409116/ Placebo in the study unit [(dd)]		X	X	X		X		X			
Review of subject diary (review of subject dosing record), IP accountability and compliance check [(ee)]			X	X		X		X			X
Dispensing of subject diary [(ff)]		X	X	X		X					
Dispensing of Patient's card		X									

Protocol activity	Screening	Treatment Period							Follow UP	End of Study	Early Withdrawal
Visit No	1	2	3	4	5	6	7	8	9	10	
Study Day/ Week	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit						N/A	±2 Days based on Week 0/Day 1 visit		
Investigational Product Dispensing [gg]		X	X	X		X					
Prior/Concomitant Medication & Treatments	X →	X →	X →	X →	X →	X →	X →	X →	X →	X →	X →
Hospitalization [hh]								X →			
Discharge from the study										X	X
Randomisation[ii]	X										

Abbreviations: → ongoing/continuous event; ACR = American College of Rheumatology; ACPA = anti-citrullinated protein autoantibodies; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; EW = early withdrawal; ESR = Erythrocyte Sedimentation Rate; FACIT-Fatigue Scale = Functional Assessment of Chronic Illness Therapy fatigue scale; FSH = follicle stimulating hormone; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBV DNA= hepatitis B DNA; HCVAb = hepatitis C antibody; HCV RNA=hepatitis C RNA; HIV = human immunodeficiency virus; IP = investigational product; PAAP = Patient Assessment of Arthritis Pain; PtGA = patient global assessment; PhGA = Physician Global Assessment; RA = Rheumatoid arthritis; WONCBP = women of non-childbearing potential.

Footnotes to Table 1.

a. Visits should occur when scheduled. Apart from ambulatory visits phone call visits will be performed to monitor adverse events and compliance.

b. Patient who withdraws from the treatment period should undergo the procedures for an early withdrawal visit and return for follow up visits as in Protocol indicated and medically indicated in the opinion of the Principal Investigator.

c. RA medications taken before and after informed consent are signed and verified during the Screening Period.

d. Vital Signs include: blood pressure, pulse, and body temperature measured after approximately 5 minutes of rest. Vital signs will be assessed during the screening period, on Day 1/ Baseline; Day 8; 29; 57; 85; 99; 113 and in case of early withdrawal. Vital signs measurement may be performed as well at other times, at the discretion of the Investigator if there were findings during a previous examination or in the case of a new/open adverse event (AE).

e. Complete Physical Examination should take place at Screening, Day 1/ Baseline and next during the Follow- up period (Day 99), at the end of the study (Day 113) and in case of early withdrawal.

f. Targeted Physical Examination should be performed on Day 8; 57 and 85.

g. An ECG is to be performed during the screening period and next on Day 1/ Baseline, Day 8, Day 85, Day 113 and in case of early withdrawal. The ECG procedure may be performed as well at other times, at the discretion of the Investigator if there were findings during a previous examination or in the case of a new/open adverse event (AE).

h. Chest radiograph (posterior-anterior and lateral views are recommended, however local guidelines should be followed) is required at Screening. A chest Xray or other appropriate diagnostic imaging modality (ie, CT or MRI) performed within 12 weeks prior to Screening and read by a qualified radiologist with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy may substitute for the chest X-ray taken at Screening. Documentation of the official reading must be located and available in the source documentation.

i. Laboratory tests may be repeated once during the screening period; the last value will be used to determine eligibility. Single repeats of laboratory tests are consisted of Blood Chemistry, Haematology, Coagulation, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Anti CCP Antibodies (ACPA) and Urinalysis.

j. Blood Chemistry, Haematology, Coagulation will be tested at Screening and next on Day 1/Baseline; 8; 29; 57; 85; 99; 113 and in case of early withdrawal.

k. RF parameter is to be evaluated at Screening, on Day 1/ Baseline; Day 8, 29, 57, 85, during the Follow up visits: Day 99; at the end of the study (Day 113)and in case of early withdrawal.

l. C- reactive protein (CRP) will be assessed at Screening and on Day 1/Baseline; 8; 29; 57; 85; 99; 113 and in case of early withdrawal. If patient's CRP level is below 7 mg/L on Screening visit, it is possible to perform CRP measurement once again within 28 days of Screening period, provided at least 14 days since initial CRP measurement and prior to Day -5 before Baseline.

m. ESR will be performed during the screening period and during the treatment period: on Day 1; 8, 29, 57, 85 and during the follow up visits: Day 99; at the end of the study (Day 113) and in case of early withdrawal.

n. ACPA is to be assessed at Screening; Day 1/ Baseline; Day: 29, 57, 85, 113 and in case of early withdrawal.

o. Fasting lipid profile is to be assessed at Screening, Day1/Baseline, Day: 8, 29, 57, 85, 99, 113 , and in case of early withdrawal(samples must be collected after a minimum 6-hour fasting), and includes: fasting total cholesterol, LDL, HDL, triglycerides.

p. Blood pregnancy test must be negative prior to randomization at Screening.

q. Serum FSH concentration is to be measured at Screening among women of non-childbearing potential only.

r. Urinalysis consists of general urine test and urine sediment test will be performed at Screening; on Day 1/ Baseline; 8; 29; 57; 85; 99; 113 and in case of early withdrawal.

s. Urine pregnancy test is to be performed on Day1/Baseline, 8; 29; 57; 85; 99; 113 and in case of early withdrawal.

t. Subjects will be questioned about used contraception methods at Screening; on Day 1/ Baseline; 8; 29; 57; 85; 99; 113 and in case of early withdrawal.

u. Subjects will be screened for hepatitis B virus infection and will be excluded if positive for hepatitis B surface antigen (HBsAg). A positive result for antiHBc antibodies in subjects negative for HBsAg requires HBV DNA testing. A positive test result for HBV DNA will be exclusionary. For subjects who are negative for HBsAg and anti-HBc antibodies and has had a HBV vaccination a positive test result for anti-HBs antibodies is expected – such subjects may be enrolled without HBV DNA testing. Enrolled subjects positive for anti-HBc antibodies and/or anti-HBs antibodies (except for vaccinated subjects negative for anti-HBc antibodies and positive for anti-HBs antibodies) will have repeated HBV DNA testing at week 6 (or early termination visit) and last follow-up visit. A positive result for HBV DNA testing in these subjects will require immediate interruption of study drug and a hepatologist consultation. Subjects who are seropositive for antibodies to hepatitis C virus (at screening) may be allowed to participate in the study provided they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to screening, and have a third negative HCV RNA test result at screening.

v. Human immunodeficiency virus (HIV) testing is mandatory. Test result must be negative at Screening before randomization.

w. Subjects with a positive documented IGRA TB test (eg, QuantiFERON□-TB GOLD (QFT-G) performed within 12 weeks prior to Screening are excluded. A subject who is currently being treated for either latent or active TB infection is to be excluded. Patients will be verified in terms of previous and current infection status during the screening period.

x. The PCR test for SARS-CoV-2 will be performed at Screening, 72 hours before Day 1. Subjects with a positive result of the test will be excluded from the study. Any symptoms suggestive of COVID-19 during the study must be verified in a study unit. In case of a positive result of the PCR test, CPL409116 administration must be ceased and isolation/quarantine is recommended in accordance with local sanitary regulations. After early withdrawal from the study due to SARS-CoV-2 infection participants will be monitored via phone call visits according to the study schedule up to the end of the study or, if needed trough two weeks after the end of the study. In case of early withdrawal it is highly recommended to call on a participant to come to the study unit for the last control visit after the end of infection or in case of a negative result of the PCR test. Not vaccinated participants who live with a person infected with SARSCoV-2 will be excluded from the study due to obligatory quarantine. It is necessary to fill in questionnaire by a participant regarding potential SARS-CoV-2 infection within 14 previous days at Screening visits and at the beginning of every ambulatory visit during the treatment and follow-up period.

y. Toxicology tests including alcohol breath tests and urine drug tests will be performed at Screening; on Day 1/ Baseline; 8; 29; 57; 85; 99; 113 and in case of early withdrawal.

z. Adverse events will be monitored during the entire study period starting with the Screening Period and ending with the last visit on Day 113 (Week 16). Control will take place during ambulatory visits, in case of the early withdrawal visit and adverse events will be verified with phone call visits.

aa. Blood samples for PK analysis are to be collected on the following Days: 1/Baseline; 8; 57 (timepoints: pre-dose (≤5 minutes prior to CPL409116 administration); 0.5h; 1.0h; 1.5h; 2.0h; 2.5h; 3.0h; 4.0h; 6.0h after CPL409116 administration) and on Day 29 in the following timepoints: pre-dose (≤5 minutes prior to CPL409116 administration) and 2.5h after CPL409116 administration. On Day 85 PK blood sample collection is to be carried out in 13 timepoints, as follows: pre-dose (≤5 minutes prior to CPL409116 administration); 0.5h; 1.0h; 1.5h; 2.0h; 2.5h; 3.0h; 4.0h; 6.0h; 8.0h; 10h; 12h and 24h after morning CPL409116 administration on Day 85.

[redacted]

cc. Effectiveness assessment will be performed by using clinical scales. Patients as well as Investigators will be engaged in filling out the questionnaires. Patient reported assessments, including PtGA and PAAP VAS measures and HAQ-DI questionnaires, should be performed prior to any other assessments. Questionnaires designed for patients should be filled out before the patient contact with medical staff and Investigator of a clinical unit. Additional unscheduled assessments should be performed as clinically indicated. Tender/Painful Joint Count (68) and Swollen Joint Count (66) will be performed at Screening; Day1/baseline; Day 29;57; 85; 113 and in case of early withdrawal. DAS28-CRP will be performed at Screening; Day1/Baseline; Day 29; 57; 85; 113 and in case of early withdrawal. FACIT-F (Fatigue) and SF-36 RAND will be performed on Day1/baseline; Day 85;113 and in case of early withdrawal. On study drug dosing days, assessments (including joint counts and questionnaires), and pre-dose blood collections are to be performed prior to dosing unless otherwise stated.

dd. Investigational product tablets will be administered to the subject in the clinic on the morning of clinic visits and all other dosing will be performed by the subject outside of the clinic. The last dose of CPL409116 will be administered on Day 85 in the morning. Nightly CPL409116 dose on Day 85 is to be skipped.

ee. Review of subject diary (review of subject dosing record), IP accountability and compliance check is to be performed on Day 8; 29; 57 and 85 and in case of early withdrawal.

ff. Subject diary dispensed and/or collected. Subject diary will be dispensed on Day 1; 8; 29 and 57. Subject diary will be collected on Day 8; 29; 57 and 85. gg. Investigational product will be dispensed during ambulatory visits on the following Days: 1/Baseline; 8; 29 and 57. Empty blisters will be collected on Days: 8; 29; 57 and 85.

hh. Hospitalization will take place on Day 85 up to Day 86 in the morning due to PK blood sample collection in 13 timepoints, as follows: pre-dose (0.0); 0.5h; 1.0h; 1.5h; 2.0h; 2.5h; 3.0h; 4.0h; 6.0h; 8.0h; 10h; 12h; 24h (Day 86) after morning CPL409116 administration on Day 85. Subjects are to be hospitalized from Day 85 up to Day 86 in the morning or spend the night (Day 85/ Day 86) outside of the clinic but return to the study centre on Day 86 in the morning to donate the last blood sample 24h (+/-5 min) after morning CPL409116 administration on Day 85.

ii. Randomisation is to be performed at the end of the Screening. It will be the last procedure of the screening period after fulfilment of all inclusion criteria and none of exclusion criteria.

jj. Follow-up ambulatory visits for each subject are to take place at Week 14 and 16 (Day 99 and 113 Day). Follow-up telephone contacts are to take place at Week 13, and Week 15 (Day 92 and 106 respectively).

2.3. Sample size

Sample size calculation for a trial with a continuous outcome measure defined as change from baseline was determined based on simulation of analysis of covariance (ANCOVA) where the baseline measure, treatment and clinical site are included as covariates in the analysis. The value assumptions were adopted from a published data. The outcome measure DAS28-CRP, measured at baseline and at 12-week postintervention. A decrease in the DAS28-CRP score indicates an improvement in health status. Assuming the baseline mean scores are the same for drug and placebo arms and equal to 5. 5 (with standard deviation equal to 1.0). We assume 12-week mean score for drug equal to 3.7 (SD = 1.1) and for placebo 4.5 (SD = 1.1). With 21 patients per group, the study has >80% power to detect an difference of 0.8 points or greater compared to placebo, given 5% significance level. Assuming a 16% dropout rate the study will enroll approximately 100 subjects.

3. General aspects of the statistical analysis

3.1. Analysis populations

The following populations are to be analyzed:

- Full Analysis Set (FAS): All randomized patients.
- Intent to Treat Set (ITT): All randomized patients that received at least 1 dose of IMP (60 mg, 120 mg, 240 mg CPL409116 or placebo) and have completed baseline assessments allowing for calculation of DAS28-CRP score. Subjects will be grouped according to treatment as randomized. This will be the main population used for analysis.
- Per Protocol Set (PP): Patients from the FAS who complete the Treatment Period (Day 85) without a major protocol deviation. Protocol deviations will be determined before unblinding.
- Safety Analysis Set (SS): All patients who receive at least 1 dose of IMP (60 mg, 120 mg, 240 mg CPL409116 or placebo).
- Pharmacokinetic Set (PS) – all patients dosed with CPL409116 with at least 1 PK parameter evaluable.
- Pharmacokinetic Set for parameter calculation (PSPC): All patients dosed with CPL409116 with at least 1 PK parameter evaluable and without any major protocol deviation during Treatment Period thought to interfere with the absorption, distribution, metabolism, and excretion of CPL409116.

The FAS will be used for demographic and other baseline characteristics. The ITT will be the primary analysis set used for all efficacy analyses and the PP will be employed for supportive analyses of the primary and secondary efficacy endpoints. Patients will be included in the treatment group they were randomized to. The SS will be used for all safety analyses and patients will be included in the treatment group based on the treatment they actually received. PS and PSPC will be used for pharmacokinetic analyses, including exploratory pharmacokinetic analyses. [redacted]

3.2. Definition of subgroups

Analysis of primary and secondary endpoints will be provided for ITT and PP populations by the following subgroups:

- Age (<57 years old vs ≥57 years old)

- Sex (male vs. female)
- Disease severity based on DAS28-CRP score at baseline (moderate vs. high).

3.3. Protocol deviations

All protocol deviations will be listed by subject. These deviations will be handled in accordance with the Contract Research Organization's (CRO) SOPs.

For the allocation of patients to analysis populations, all protocol deviations will be reviewed according to the criteria specified below. A comprehensive data review plan, to be finalized before the data review meeting, will detail these criteria and outline all necessary data and listings for an exhaustive assessment of protocol deviations.

The determination of major and minor protocol deviations will be performed during the data review meeting in which key stake-holders will participate. The proceedings and decisions of this meeting will be documented in the data review meeting minutes. This document will be finalized prior to the unblinding of the treatment group for the main analysis of data.

The following protocol violations are defined as major and will thus lead to the exclusion of a patient from the PP population:

Table 2. Protocol deviations

Number	Major protocol deviation	Reasons for exclusion from PP population
1	No valid assessment of DAS28-CRP at Day 1 (Baseline)	X
2	No valid assessment of DAS28-CRP at Day 85 (Week 12)	X
3	Any violation that have a major impact on DAS28-CRP assessment, not limited to in- or exclusion criteria	X
4	Dose or administration of study medication deviates substantially from protocol schedule	X

3.4. Interim analyses

No formal interim analysis is planned.

3.5. Timing of analyses

Data analysis will be performed after all the data will be completed, verified, whole database will be locked and unblinded, with the exception of PK and PD analyses, which will be analysed after the end of the treatment period of all study participants.

4. Statistical analysis specification

4.1. General

Statistical significance level will be equal to 0.05. P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

4.2. Definitions/derived variables

Unless otherwise specified, baseline is defined as value collected closest but not later than time of the first IMP administration (Day 1 Baseline).

As most of the procedures on Day 1 Baseline are performed before IMP administration, values for following forms will be used as baseline:

- TJC/SJC/DAS-28 CRP on Day 1 Baseline,
- Patient Assessment of Arthritis Pain (PAAP) on Day 1 Baseline,
- Patient's Global Assessment of Arthritis (PtGA) on Day 1 Baseline,
- Physician Global Assessment of Arthritis (PhGA) on Day 1 Baseline,
- Health Assessment Questionnaire – Disability Index (HAQ-DI) on Day 1 Baseline,
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) on Day 1 Baseline,
- 36-Item Short Form Survey Instrument (SF-36) on Day 1 Baseline,
- Vital signs on Day 1 Baseline,
- Clinical laboratory data (hematology, biochemistry, urinalysis, lipid profile, coagulation profile, rheumatoid biomarkers indicators) on Day 1 Baseline,
- 12-lead ECG on Day 1 Baseline,
- PK blood sample collection [predose] on Day 1 Baseline,
- [redacted]

4.2.1. Day 1 and relative study days

Day 1 is defined as the day of the first administration of study medication (reference date). In general, any date provided in patient listings will be presented as study day (in addition to the date provided): If a date is later than the reference date then the study day is calculated as:

study day = date - reference date +1.

If a date is prior the reference date then the study day is a negative number calculated as

day = date - reference date.

No study day 0 will exist.

4.2.2. BMI

BMI is calculated according to the equation:

$$BMI = \text{weight [kg]} / \text{height [m]}^2$$

BMI will be subsequently categorized using following ranges:

<18.5 – Underweight

<18.5 – 25) – Normal weight

<25 – 30) – Overweight

≥30 – Obese.

4.2.3. Amount of cigarettes smoked – pack-years

It is assumed that pack of cigarettes contains 20 items.

Number of cigarettes per day will be calculated following conversion table.

Table 3. Conversion to number of cigarettes smoked per day

Unit	Frequency	Multiplier
Cigarettes	Daily	1
	Every week	0.1429
	Every month	0.0329
	Per year	0.0024
Packs	Daily	20
	Every week	2.8571
	Every month	0.6571
	Per year	0.0548

Note: Length of year – 365.25 days, length of month – 30.4375 days.

If start or end date of smoking is missing or partially missing the imputation of dates described in section 4.6 will be used.

Duration of smoking will be calculated as follows:

If former smoker:

Duration in years = (End date of smoking - Start day of smoking)/365.25.

If current smoker:

Duration in years = (Date of screening visit - Start day of smoking)/365.25.

Pack years will be calculated as follows:

Number of pack-years = (number of *cigarettes* smoked per day/20) * number of years smoked.

4.2.4. Duration of rheumatoid arthritis

Duration of rheumatoid arthritis will be calculated as:

Duration of rheumatoid arthritis = (date of signature of ICF – date of rheumatoid arthritis diagnosis)/365.25,

where ICF is Informed Consent Form.

For partial dates imputation described in section 4.6 will be used prior to duration calculation.

4.2.5. Duration of methotrexate treatment

Duration of methotrexate treatment will be calculated as:

Duration of methotrexate treatment = (date of signature of ICF – start date of methotrexate treatment)/365.25,

where ICF is Informed Consent Form.

For partial dates imputation described in section 4.6 will be used prior to duration calculation.

4.2.6. Treatment exposure and treatment compliance

Drug exposure is the total number of days the patient takes study drug during the overall study period (not including interruptions). Exposure to IMP will be calculated as:

Exposure = (Last IMP dose – First IMP dose) + 1 - sum of interruptions

Extent of exposure will be calculated as a sum of exposures of all patients and expressed in patient-treatment years:

Extent of exposure [patient months] = sum(Exposure)/30.44.

Drug adherence will be assessed based on patient's diary and calculated as:

Drug adherence [%] = Number of compliant doses taken/Number of doses to be taken 100%*

A single dose is to be consider as a compliant when all 4 tablets are administered. Number of doses to be taken is equal to 169 (84 days * 2 + 1).

A patients is to be considered as a complier with dosing regimen when at least 80% of the doses are compliant (136 doses).

4.2.7. DAS28-CRP

Results of DAS28-CRP are calculated directly in the eCRF and validated according to the Data Validation Plan, so no additional derived variables are necessary.

For clarity, formula used for DAS28-CRP in the eCRF is shown here:

$$DAS28\text{–}CRP = 0.56 * \sqrt{t28} + 0.28 * \sqrt{s28} + 0.36 * \log(CRP + 1) + 0.014 * pgh + 0.96$$

Where:

t28 – sum of tender joints

s28 – sum of swollen joints

CRP – concentration of CRP protein expressed in mg/l.

Classification of disease activity is performed in the eCRF based on the following DAS28-CRP breakpoints:

<3.2 – Low disease activity

<3.2 – 5.1> – Moderate disease activity

>5.1 – High disease activity

Moreover, DAS28-CRP score lower than 2.6 will be classified as remission.

4.2.8. Response states classified by change in DAS28-CRP

Based on DAS28-CRP score subjects can be classified into following response states:

- Good responder: improvement of more than 1.2 on DAS28-CRP score and a present score of at maximum 3.2.
- Moderate responder: improvement of more than 0.6 but no more than 1.2 and a present score of at maximum 5.1 OR improvement of more than 1.2 and a present score more than 3.2.
- Non-responder: improvement of no more than 0.6 OR improvement of more than 0.6 but no more than 1.2 and a present score of more than 5.1.

4.2.9. DAS28-ESR

For additional analysis DAS28-ESR is calculated according to the formula (Leong et al, 2020):

$$DAS28\text{–}ESR = 0.56 * \sqrt{t28} + 0.28 * \sqrt{s28} + 0.7 * \log(ESR) + 0.014 * pgh$$

Where:

t28 – sum of tender joints

s28 – sum of swollen joints

ESR – erythrocyte sedimentation rate [mm].

4.2.10. Health Assessment Questionnaire – Disability Index (HAQ-DI)

Results of HAQ-DI are calculated directly in the eCRF and validated according to the Data Validation Plan, so no additional derived variables are necessary.

4.2.11. 36-Item Short Form Survey Instrument (SF-36 RAND)

Results of SF-36 RAND are calculated directly in the eCRF and validated according to the Data Validation Plan, so no additional derived variables are necessary.

4.2.12. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

Results of FACIT-F are calculated directly in the eCRF and validated according to the Data Validation Plan, so no additional derived variables are necessary.

4.2.13. American College of Rheumatology assessment (ACR)

The American College of Rheumatology's (ACR20) definition for calculating improvement in RA is calculated as:

- A 20% improvement in tender joint count (68),
- A 20% improvement in swollen joint count (66),
- A 20% improvement in at least 3 of the following 5 remaining ACR-core set measures:
  - patient global assessments (PtGA),
  - physician global assessments (PhGA),
  - pain (PAAP),
  - disability (HAQ-DI),
  - an acute-phase reactant (CRP).

Similarly, ACR50, ACR70 and ACR90 are calculated with the respective percent improvement.

Improvement in each of those measures will be calculated as:

*Measure improvement = (Measure at Visit - Measure at Day 1)/Measure at Day 1 * (-100%)*

As in all of those ACR-core set measures improvement is defined as lower value of the measure, in the equation above there is multiplication by minus 100%, so the result would be informing about improvement percentage.

4.2.14. Targeted medical adverse events

Any of the AEs that occurred on (or after) the day of the first IMP administration that meets one of the following criteria:

SOC belongs to group "Infections and infestations"

OR HLGT belongs to a group "Embolism and thrombosis"

OR PT is "Gastrointestinal perforation"

OR (SOC belongs to a group "Cardiac disorders" AND AE is classified as Serious).

OR SOC belongs to group "Neoplasms benign, malignant and unspecified (incl cysts and polyps)"

OR PT is "Hypotension"

OR PT is "Blood pressure abnormal"

where:

PT – MedDRA Preferred Term

HLGT – MedDRA High Level Group Term

SOC – MedDRA System Organ Class.

Preliminary list prepared by the data management team will be reviewed by medical monitor and confirmed during blinded data review meeting.

4.2.15. Laboratory values

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½*LLOQ and those greater than upper limit of quantification will be set to this limit.

4.2.16. Prior, rescue and concomitant medication

Prior medications are those with an end date of administration prior to the date of the first IMP administration.

Concomitant medications are those that started or continued during the study treatment period.

List of drugs classified as rescue medications will be prepared based on assessment performed by Medical Monitor and presented during BDRM.

Classification of drugs into Disease-Modifying and Anti-Rheumatic Drugs (DMARDS), glucocorticosteroids, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) will be based on ATC codes presented below. This list may be updated before the final database lock by a medical monitor.

Table 4. Prior medication classification for purpose of baseline characteristics

ATC code for the group	ATC code for the group	ATC code for cmpd	Name
c/tsDMARDS	A07EC Aminosalicylic acid and similar agents	A07EC01	sulfasalazine
	L01BA Folic acid analogues	L01BA01 (iv)	methotrexate
	L04AA - Selective immunosuppressants;	L04AA01	cyclosporine
		L04AA13	leflunomide
	L04AX - Other immunosuppressants	L04AX01	azathioprine
		L04AX03 (oral)	methotrexate
	M01CB Gold preparations;	M01CB01	sodium aurothiomalate
		M01CB03	auranofin
		M01CB04	aurothioglucose
	P01BA - Aminoquinolines	P01BA02	hydroxychloroquine
bDMARDS	L04AA - Selective immunosuppressants	L04AA11	etanercept
		L04AA12	infliximab
		L04AA14	anakinra
		L04AA17	adalimumab

		L04AA24	abatacept
	L04AB - Tumor necrosis factor alpha (TNF-α) inhibitors	L04AB05	certolizumab
		L04AB06	golimumab
	L04AC - Interleukin inhibitors	L04AC07	tocilizumab
	L01XC - Monoclonal antibodies	L01XC02	rituximab
ATC code for the group	ATC code for the group	ATC code for cmpd	Name
Glucocorticosteroids	H02AB	H02AB04	methylprednisolone
		H02AB06	prednisolone
		H02AB07	prednisone
		H02AB13	deflazakort
ATC code for the group	ATC code for the group	ATC code for cmpd	Name
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	M01AA - Butylpyrazolidines	M01AA01	phenylbutazone
	M01AB - Acetic acid derivatives and related substances	M01AB01	indometacin
		M01AB02	sulindac
		M01AB03	tolmetin
		M01AB05	diclofenac
		M01AB08	etodolac
		M01AB15	ketorolac
		M02AA25	Aceclofenac
		M01AB55	diclofenac in combination
	M01AC - Oxicams	M01AC01	piroxicam
		M01AC02	tenoxicam
		M01AC05	lornoxicam
		M01AC06	meloxicam
	M01AE - Propionic acid derivatives	M01AE01	ibuprofen
		M01AE02	naproxen
		M01AE03	ketoprofen
		M01AE04	fenoprofen
		M01AE09	flurbiprofen
		M01AE11	tiaprofenic acid
		M01AE12	oxaprozin
	M01AG - Fenamates	M01AG01	mefenamic acid
	M01AH - Coxibs	M01AH01	celecoxib
		M01AH05	etoricoxib
		M01AH02	rofecoxib
		M01AH03	valdecoxib

	M01AX - Other antiinflammatory and antirheumatic agents, non-steroids	M01AX01	nabumetone
	M02AA Antiinflammatory preparations, non-steroids for topical use	M02AA26	nimesulide
	M02AC - Preparations with salicylic acid derivatives	M02AC	preparation with salicylic acid derivations

4.2.17. Pharmacokinetic and pharmacodynamic parameters

The pharmacokinetic parameters will be computed using non-compartmental modelling approach using actual sampling times. The pharmacokinetic parameters will be derived individually for each subject and day of study, if applicable.

PK parameters listed below will be estimated for both CPL409116 and its metabolite M3, if data permits.

PK parameters listed in the Clinical Trial Protocol:

- $AUC_{(0\text{-}6h)}$: The area under the curve of plasma concentration vs time, from time point zero up to 6 hours after drug administration, unit: [ng*h/mL]. $AUC_{(0\text{-}6h)}$ will be calculated according to the linear trapezoidal rule. To be calculated for Days 1, 8, 57 and 85.
- C_{max}: Maximum plasma concentration, unit: [ng/mL]. C_{max} defines the maximum concentration of the drug substance (or metabolite) in plasma during administration period. C_{max} will be obtained directly from the measured concentrations. If multiple peaks occur, the highest postdose concentration will be reported as C_{max}. To be calculated for Days 1, 8, 57 and 85.
- T_{max}: Time to reach maximum plasma concentration, unit: [h]. T_{max} will be obtained directly from the actual sampling times. In the case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported. To be calculated for Days 1, 8, 57 and 85.
- K_{el}: Terminal elimination rate constant, unit: [1/h]. K_{el} will be estimated via linear regression of time versus log of concentration. This parameter will be calculated by linear least squares regression analysis using at least last three non-zero plasma concentration values. C_{max} values will not be included in K_{el} calculation. K_{el} will only be calculated the adjusted coefficient of determination of exponential fit (R^2 adjusted) is not less than 0.7 ($R^2 \geq 0.7$). To be calculated for Days 1, 8, 57 and 85.
- $T_{1/2}$: Plasma elimination half-life, unit: [h]. $T_{1/2}$ will be calculated as $\ln(2)/K_{el}$. To be calculated for Days 1, 8, 57 and 85.

Exploratory PK parameters:

- $AUC_{(0\text{-}inf)}$: The area under the curve of plasma concentration vs time, from time point zero extrapolated to infinity, unit: [ng*h/mL]. $AUC_{(0\text{-}inf)} = AUC_{(0\text{-}t)} + C_t/K_{el}$, $AUC_{(0\text{-}t)}$ is the area under the curve of plasma concentration vs time from time point zero to the last measurable analyte concentration in plasma, C_t is the last measurable analyte concentration in plasma and K_{el} is the terminal elimination rate constant. To be calculated for Days 1, 8, 57 and 85.
- $AUC_{(0\text{-}t)}$: The area under the curve of plasma concentration vs time, from time point zero to the last measurable analyte concentration in plasma, unit: [ng*h/mL]. $AUC_{(0\text{-}t)}$ will be calculated according to the linear trapezoidal rule. To be calculated for Days 1, 8, 57 and 85.
- AUC_{tau}: The area under the curve of plasma concentration vs time, from dosing time to dosing time plus tau (12 h), unit: [ng*h/mL]. AUC_{tau} will be calculated according to the linear trapezoidal rule. To be calculated for Day 85. If dosing time plus tau is not an

exact observation time due to small sampling time deviations, the AUC_{tau} is computed based on an estimated concentration at dosing time plus tau (concentration at dosing time plus tau is estimated using logarithmic interpolation if both observed analyte concentrations last before and first after the time point dosing time plus tau are measurable (>LLOQ) and using the linear interpolation otherwise).

- t_{lag}: Time to measurable (non-zero) plasma concentration, unit: [h]. t_{lag} will be obtained directly from the actual sampling times as the last sampling time prior to the first measurable (non-zero) plasma concentration. To be calculated for Day 1.
- CL/F (where F is product absolute availability in oral administration): apparent systemic clearance, will be calculated as dose administered in dosing interval divided by AUC_{tau} at steady state (Day 85), CL/F = Dose/AUC_{tau}. To be calculated for Day 85.
- MRT: Mean Residence Time will be calculated for Day 85 as ratio of $AUMC_{0\text{-}inf}$ to the AUC_{tau}, where $AUMC_{0\text{-}inf}$ = $AUMC_{tau}$ + tau($AUC_{0\text{-}inf}$ - AUC_{tau}), where C_t is the last measurable concentration, t_z is time of last measurable concentration. To be calculated for Day 85. MRT will be calculated under assumption that mean input time is 0.
- V_z/F: apparent volume of distribution, calculated as Dose/(K_{el}*(AUC_{tau})] at steady state (Day 85) (with limitations as described above). To be calculated for Day 85.
- C_{trough}: the trough concentration is the concentration reached by the drug immediately before the next dose is administered or at 12 h for the last dose. To be calculated for Days 8, 29, 57, and 85. Note: sampling time of 12 h on Day 85 should also be included.
- $C_{max,ss}$: Maximum blood concentration obtained directly from the measured concentration, at steady state - equivalent to the C_{max} for the Days 8, 57, and 85. To be calculated for Days 8, 57, and 85.
- $C_{min,ss}$: Minimum blood concentration obtained directly from the measured concentration, at steady state. To be calculated for Days 8, 29, 57, and 85.
- C_{av}: average concentration in the dosing interval, calculated as $AUC_{tau,}$/12 h. To be calculated for Day 85.
- Swing: calculated as ($C_{max,ss}$-$C_{min,ss}$)/$C_{min,ss}$ x 100%. To be calculated for Days 8, 57, and 85.
- Fluctuation: calculated as ($C_{max,ss}$-$C_{min,ss}$)/C_{av} x 100%. To be calculated for Day 85.
- Accumulation ratio for $AUC_{(0\text{-}6h)}$: ratio of $AUC_{(0\text{-}6h)}$ on the selected day (d) to the value for Day 1 calculated as $AUC_{(0\text{-}6h,d)}$/$AUC_{(0\text{-}6h,\ 1)}$. To be calculated for Days 8, 57, and 85.
- Accumulation ratio for C_{max}: ratio of C_{max} on the selected day (d) to the value for Day 1 calculated as $C_{(max,d)}$/$C_{(max,\ 1)}$. To be calculated for Days 8, 57, and 85.
- AUC_%Extrap_obs: The percentage of residual area is to be determined by the formula [($AUC_{(0\text{-}inf)}$-$AUC_{(0\text{-}t)}$]/$AUC_{(0\text{-}inf)}$ x 100%. To be calculated for Days 1, 8, 57, and 85.

[redacted]

4.3. Specifications for summary tables

For **continuous variables**, summary statistics will generally consist of sample size (N), number of missing values, arithmetic mean, standard deviation (SD), median, lower (Q1) and upper (Q3) quantile, minimum, and maximum. Summaries of PK and PD variables will, in addition, contain the geometric mean and the coefficient of variation.

Binary/categorical variables will be summarized and displayed in frequency tables showing sample size, absolute and relative frequencies.

In general, data will be included in summary tables stratified by randomized treatment group.

4.4. Specifications for plots

Unless otherwise specified, plots for continuous variables will present mean and SD for each randomized treatment group. LS means calculated from MMRM models will be presented as bars with whiskers representing 95% confidence intervals (CI). Binary endpoints will be presented as forest plots – with a point representing proportion of subjects meeting the endpoint and whiskers representing a 95% CI. Results from logistic regression will also take form of a forest plot – point with whiskers, where point represents odds ratio and whiskers confidence interval.

Time to remission will be presented graphically using Kaplan-Meier curve – a series of declining horizontal steps.

For safety analysis distribution of data will be presented as line and point and whisker plots (presenting mean and standard deviations) or boxplots (for variables with highly skewed distributions – such as CRP). For boxplot top and bottom of the box will represent lower and upper quartile respectively. Thick line in the middle of the box will be median. Whiskers will represent the lowest value at most Q1-1,5*IQR (inter quantile range) and the largest value no further than Q3+1,5*IQR. Points will represent potential outliers. Treatment groups will be presented as separate panels within a figure.

Data will be shown for each randomized treatment group. Data collected during unscheduled visit will not be shown on plots unless otherwise specified.

4.5. Data listings

Data on listings will be listed as documented. Relevant generated and transformed variables will be listed next to the original data items. Any imputed value will be flagged.

In all listings the patient identifier and the randomized treatment group will be included. The patient identifier consists of the center and the patient number, additionally a flag specifying analysis set will be provided. In general, patient listings will be sorted by patient identifier and visit (if applicable), unless otherwise stated.

Patient listings of data that is collected independently from visits (e.g. adverse events, medical histories or medication) will be sorted by patient identifier, day of onset or start day of administration, duration and MedDRA preferred term or base substance name, respectively.

Missing values in the listings will be represented as NA (not available) for both text and numerical data. In case of partially missing dates (when day or day and month is unknown) missing data will be represented as series of 9s – for example 2022-03 will be presented as 2022-03-99. Any imputed data will be presented separately from raw data or flagged accordingly in order to be able to review all data as collected.

4.6. Handling of withdrawals, missing values and outliers

For the main analyses performed using the ITT and PP populations, data will be analyzed as observed during the study, no imputation rule will be applied.

A sensitivity analysis will be conducted for primary and secondary efficacy endpoints, whereby missing data are imputed using last observation carried forward method (LOCF) for continuous endpoints and non-responder imputation (NRI) method for binary endpoints.

In pharmacokinetic analyses, missing drug concentration data (no value, not available, NA) will be omitted from PK calculations. Drug concentration data below LLOQ will be treated in pharmacokinetic analysis as follows:

- If the concentration below LLOQ is recorded after the last measurable concentration in the dosing interval, then it is omitted from area calculations and elimination phase analysis.
- In other cases the concentration below LLOQ concentration value is set to zero.
- If an entire concentration-time profile below LLOQ, the profile will be excluded from the PK analysis.

For descriptive statistics of drug concentrations and calculation of PK parameters obtained directly from the observed concentrations (including C_{max}, $C_{min,ss}$, $C_{max,ss}$, C_{trough}) values below LLOQ will be set to zero.

[redacted]

A worst-case scenario will be used in the estimation of partial dates such as adverse events, medical history, rheumatoid arthritis history, smoking history or concomitant medications. That is, for an incomplete start date the first day of the month or the first month of the year will be used. For an incomplete stop date the last day of the month or the last month of the year will be used. If an estimated start date of event is earlier than the date of day 1 or the start date is completely missing, day 1 will be used, unless documented data does not allow for this interpretation.

If start date of smoking is completely missing, it will be replaced with the date of 18th birthday. For completely missing stop date of smoking, date when informed consent was signed will be used.

Whenever estimated dates will be calculated, the incomplete date will be listed and the study day will be calculated using the estimated date. These study days will be flagged as estimated in listings with a star (*) symbol.

For other situations regarding missing data not mentioned in this document, missing data will generally not be replaced or imputed.

4.7. Disposition of patients

The number of patients screened, the number of patients randomized and the number of patients in each analysis population will be summarized. The reasons for exclusion from each analysis population will be summarized for all patients randomized. The reasons for non-eligibility for randomization, i.e. the violated inclusion or exclusion criteria will be listed for all non-randomized patients by visit.

Major protocol deviations (leading to the exclusion from the PP) and minor protocol deviations (not leading to the exclusion from the PP) will be summarized for the safety population. The determination of major and minor protocol deviations will be performed during the blind data

review meeting documented in the blind data review meeting minutes, which will be finalized prior to unblinding of the treatment group for the main analysis of data of the double-blind treatment.

The number of patients who completed the study and the number of patients who terminated the study early will be summarized in frequency tables for the safety, the FAS, the ITT and the PP populations.

The timing of early termination will be summarized for each study month for the safety, the FAS, the ITT and the PP populations.

Consolidated Standards of Reporting Trials (CONSORT) diagram (Moher et al. 2001) will be used to present abovementioned data in a graphical form.

4.8. Demographic and baseline variables

Demographic data and other baseline characteristics will be summarized for Safety, FAS, ITT and PP population by treatment group and overall. Separate tables for Safety and ITT populations will be prepared when number of patients in those populations will differ from FAS population. The following variables will be summarized:

- Age (years) as continuous variable [(date of ICF signature – date of birth)/365.25]
- Age category (<57/ ≥57 years old)
- Sex (male / female)
- Race
- Weight [kg] and height [cm]
- BMI [kg/m^2] calculated as Weight (kg)/[height (m)^2]
- BMI categories (Underweight/ Normal weight/ Overweight/ Obese)
- History of plasma donation (yes / no)
- History of blood donation (yes / no)
- Use of special diet (yes / no)

A separate table will summarize a history of alcohol and drug abuse and substance use history:

- History of alcohol abuse (yes / no)
- History of drug abuse (yes / no)
- Smoking (Never, Current, Former, Not collected)
- Amount of cigarettes smoked [pack-years]
- Amount of coffee consumed [cups]
- Amount of tea consumed [cups]
- Amount of energy drinks consumed [cans].

Disease characteristic will summarize:

- Duration of rheumatoid arthritis (years)
- Duration of methotrexate treatment (years)
- Tender (68) and swollen (66) joints
- DAS28-CRP assessment from screening and Day 1 baseline including disease activity categorization.

A separate table will summarize results on rheumatoid biomarkers indicators collected during screening and Day 1 baseline.

Total scores, collected during baseline, will be summarized in a table for following scales:

- Physician Global Assessment of Arthritis (PhGA)
- Patient's Global Assessment of Arthritis (PtGA)
- Patient Assessment of Arthritis Pain (PAAP)
- Health Assessment Questionnaire – Disability Index (HAQ-DI) including pain level measured with VAS.

Due to size a separate table will present subscales of 36-Item Short Form Survey Instrument (SF-36) and total score from Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F).

Separate tables will be produced for screening and baseline safety data:

- Vital signs: blood pressure [mmHg], heart rate [beats per minute], body temperature [°C] (numerical results as well as categorization of result)
- 12-lead ECG results: ECG finding, QTc Value (in ms), QRS value (in ms) – with the former two parameters presented as an average of up to three measurements at screening and one measurement thereafter).
- Physical examination (combining results from screening and baseline – in case of new abnormalities observed on Day 1, worst case will be presented in table).

Additional tables will be prepared for history of vaccination and viral serology at screening.

Other baseline characteristics will be listed only as applicable showing results for patients with abnormal results at screening or baseline.

All other screening or Day 1 safety assessments will be listed only unless specified differently below.

4.9. Medical history

Current medical conditions are defined as those entries in medical history that are ongoing at the screening visit. Medical histories and current medical conditions will be coded using a MedDRA dictionary (version of MedDRA current at the time of database lock will be used). Medical histories and current medical conditions will be summarized by treatment group and overall for the full analysis set.

Reproductive history will be listed only.

4.10. Concomitant medication

Prior and concomitant medications will be classified using information on ATC codes contained in Register of Medicinal Products Approved for Marketing on the territory of the Republic of Poland[1]. Summary of concomitant medications will be provided as count and frequency for ATC level 2 (therapeutic subgroup) and 4 (chemical subgroup). Listings of prior and concomitant medications will be provided and sorted by site, patient number, name of active substance, and date of last administration (if known). Data on methotrexate administration will be presented only in form of listing. Rescue medications will be presented in form of listing (if applicable). Information on prior use of following drug classes: glucocorticosteroids, NSAIDS

[1] https://rejestrymedyczne.ezdrowie.gov.pl/rpl/search/public

and DMARDS and will be presented as number and frequency of subjects using each class of these drugs (see 4.2.16 for definition).

4.11. Efficacy analyses

Unless otherwise specified all efficacy analyses will be performed on ITT data with sensitivity analyses performed on PP population and ITT population with data imputed using methods described in section 4.6. In addition, efficacy analyses will be performed in subgroups defined in section 3.2.

4.11.1. Primary efficacy endpoints

The main analysis will be based on ITT population with supportive analyses using PP population data and imputed ITT population as sensitivity analysis.

In order to evaluate clinical efficacy of CPL409116 at week 12 in subjects with active RA who have had an inadequate response to methotrexate a Mixed Model for Repeated Measure (MMRM) will be prepared.

A set of hypotheses (H0 – null and HA – alternative) will be tested, one for each dose level of CPL409116.

H01: The mean change at week 12 from baseline in CPL409116 at dose of 60 mg BID is the same as that observed in placebo arm.

HA1: The mean change at week 12 from baseline in CPL409116 at dose of 60 mg BID is different from that observed in the placebo arm.

H02: The mean change at week 12 from baseline in CPL409116 at dose of 120 mg BID is the same as that observed in placebo arm.

HA2: The mean change at week 12 from baseline in CPL409116 at dose of 120 mg BID is different from that observed in the placebo arm.

H03: The mean change at week 12 from baseline in CPL409116 at dose of 240 mg BID is the same as that observed in placebo arm.

HA3: The mean change at week 12 from baseline in CPL409116 at dose of 240 mg BID is different from that observed in the placebo arm.

These hypotheses will be tested using a 2-sided 5% significance level. No adjustment for multiplicity will be performed for comparisons of each concentration of CPL409116 to placebo at week 12.

Primary endpoint, change from Baseline in Disease Activity Score DAS28-CRP at Week 12, will be analyzed by MMRM model with factors for dose (placebo, 60 mg, 120 mg, 240 mg), timepoint (all measurements throughout the study will be taken into account, week 4, week 8, week 12, week 16), interaction between treatment and timepoint, clinical site, as well as baseline value of DAS28-CRP as continuous covariate. Subject will be treated as a random effect, with an unstructured covariance structure to account for the correlation among repeated measurements. If the model does not converge, another covariance structure, (e.g., AR(1), CS, etc.) will be explored. Missing data will be assumed to be missing at random. R formula which could be used for such analysis:

*mmrm(CHANGE ~ TREATMENT * TIMEPOINT* + AGE + SEX + *SITE* + *BASELINE* + *us(VISIT|ID)*

using *mmrm* function from mmrm library.

Pearson residuals will be used to identifying outlying observations and the appropriateness of the covariance structure. Normalized or scaled residuals will be used to check for normality and will be assessed graphically. Residuals from the primary model will be plotted against the predicted values and a quantile-quantile (QQ)-plot of the residuals versus the expected quantiles of the standard normal distribution will be presented.

The statistical model will allow for comparison of efficacy between placebo and 60 mg, 120 mg and 240 mg of CPL409116 at each of the timepoint. In order to compare each concentration of CPL409116 to placebo, LS means, their 95% CI, and p values will be calculated using *emmeans* function of emmeans library. Cohen's D effect size will be calculated as difference between means of given treatment arm and placebo and divided by pooled standard deviation.

Change from baseline in DAS28-CRP score at week 4, 8 and 16 will be analyzed on basis of LS-means calculated by MRMM model used in primary endpoint analysis also without adjustment for multiplicity.

Supportive analysis will be performed on PP population, as well as ITT with imputation based on last observation carried forward (LOCF) method and performed as described for the ITT population.

Sensitivity analysis of primary endpoint will include MMRM model with pooled CPL409116 arms and performed as described for the primary endpoint analysis. The only difference is that at each timepoint there will only be comparison between pooled CPL409116 and placebo. In addition, different formulation of the models will be explored (interactions between independent variables, simpler versions of the model).

4.11.2. Secondary efficacy endpoints

No correction for multiple comparisons are planned for secondary endpoints.

Proportion of subjects with DAS28-CRP remission (score < 2.6) in each study arm will be presented at any time as well as at Day 29, Day 57, Day 85 and Day 113. Proportion of subjects will be presented together with confidence intervals, difference from placebo with confidence interval and p value for comparison vs. placebo calculated using proportion test. Logistic regression model will be prepared to explain achievement of response at any time with following factors: treatment (placebo will be the reference value), country (Ukraine will be the reference value) and baseline DAS28-CRP score. Moreover, descriptive statistics for time to remission will be presented along with median time to remission estimated using Kaplan-Meier method. Each treatment arm will be compared to placebo using log-rank test.

Change from baseline in the Tender/Painful and Swollen Joint Count as well as change from baseline in PhGA will be analyzed using MMRM and performed as described for primary endpoint.

All of patient reported outcomes - change from baseline in PAAP, PtGA, HAQ-DI, SF-36 and FACIT-F will be only presented descriptively for each timepoint.

American College Rheumatology (ACR)20, ACR50, ACR70 and ACR90 responder rates will be presented in form of percentage of subjects that meets the criteria for the endpoint alongside 95% confidence interval calculated using Wilsons' method. Difference between CPL409116 arms and placebo will be presented together with confidence interval and p value calculated using proportion test. Logistic regression model will be prepared similar to the previously described endpoint of DAS28-CRP remission.

Supportive analysis will be performed on PP population, as well as ITT with imputation based on last observation carried forward (LOCF) for continuous variables and NRI method for binary endpoints and performed as described for the ITT population.

4.12. Safety analyses

Safety data will be summarized for the safety population (SS). Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only.

4.12.1. Adverse events analysis

Any undesirable signs, symptoms or medical conditions occurring or worsening of pre-existing conditions between signing informed consent and the first administration study medication are considered as pre-treatment AEs. Undesirable signs, symptoms or medical conditions or worsening of pre-existing conditions occurring after the first administration of study medication are considered as treatment emergent adverse events (TEAEs).

A TEAE will be analyzed as related to study medication (i.e. as adverse drug reaction, ADR) if the relationship to study treatment was documented as 'unlikely', 'possible', 'probable', or 'definite' or if the relationship to study treatment is missing.

An overview table presenting the incidence of the following AE categories will be presented. Percentage of patients in each category will be compared between treatments as a difference in proportions between treatments including a 95% CI based on the Agresti – Caffo method (2000):

- All AEs
- Pre-treatment AEs
- Serious AEs (SAEs) (including pre-treatment SAEs)
- Treatment emergent AEs (TEAEs)
- Treatment emergent SAEs (TESAEs)
- Severe TEAEs
- Related TEAEs
- Related severe TEAEs
- TEAEs leading to reduction of dose
- TEAEs leading to interruption of dose
- TEAEs leading to permanent discontinuation (i.e. withdrawal) of study medication
- Related TEAEs leading to permanent discontinuation of study medication
- AEs leading to death (i.e. outcome of AE is fatal)
- TEAEs leading to death
- Related TEAEs leading to death
- Targeted medical adverse events

Targeted medical adverse events are defined in section 4.2.14.

All treatment emergent AEs (TEAEs) and all serious TEAEs will be tabulated by MedDRA System Organ Class (SOC) and preferred term (PT) presenting the number and percentage of patients reporting the AE and the number of AEs reported. Additional tables will distinguish the events by whether the AE was related to study medication and by maximum severity.

All AEs documented in the eCRF will be listed by patient. Data listings will include patient ID, treatment group, verbatim term, preferred term, system organ class, start and stop date and relative day of the AE, severity, medications (yes/no), seriousness, action taken with study medication, relationship to study medication, and outcome will be provided. TEAEs will be

flagged as such. In addition, separate listings for all SAE's, deaths and AEs leading to discontinuation (action taken with study treatment = drug withdrawn or AE is reason for early termination) will be presented.

4.12.2. Safety laboratory data

Laboratory data will be summarized by type of laboratory test after all results are converted to standard SI units (according to algorithms presented in Data Validation Plan). Descriptive statistics will be calculated for each laboratory parameter at baseline (Day 1) and at each scheduled time point. Shift tables using the categories 'lower than normal range', 'within normal range' and 'higher than normal range' will be provided for each numeric parameter, comparing the baseline value to all post-baseline values. For results expressed as category (in urinalysis) shift tables will present categories: normal and abnormal. Moreover, change from baseline values will also be presented.

Other urinalysis parameters, than those pre-specified in the eCRF, will be listed only.

Listings of each laboratory parameter will be provided, marking changes from norm. A separate listings will be produced for clinically significant abnormal results (for purpose of presentation in the statistical report/CSR).

4.12.3. Vital signs

These summaries will take form of tables for raw data and changes from baseline (Day 1) as well as percentage of abnormal values.

Shift tables using the categories 'lower than normal range', 'within normal range' and 'higher than normal range' will be provided for each parameter (where applicable), comparing the baseline value to all post-baseline values. Categorization of blood pressure is performed for both SBP and DBP at once, so one shift table will be prepared only for blood pressure.

Change from baseline values in vital signs will take form of boxplots (and/or point and whisker plots) for each study arms for each vital sign parameter.

Listings flagging abnormal values will be also produced.

4.12.4. Electrocardiograms

ECG variables that will be analyzed including: QTc and QRS intervals as well as ECG findings.

ECG summaries will take form of tables for raw data and changes from baseline (values collected during Day 1) as well as percentage of abnormal values for ECG findings. In addition, shift tables presenting number of patients that either developed abnormalities since baseline will be provided.

The number of patients with at least one clinically relevant finding detected during the ECG examination will be summarized in frequency tables for each scheduled assessment or visit.

Change from baseline values of ECG parameters will take form of boxplots for each study arms.

4.12.5. Physical examination

Abnormal findings occurring after screening and baseline visit (after Day 1) will be listed. No summaries are planned.

4.12.6. Chest imaging

Method of imaging as well as date of procedure and result will be listed only. No summaries are planned.

4.12.7. Urinary test for substance abuse, alcohol breath test and pregnancy test

Data regarding urinary test for substance abuse as well as results from pregnancy test will be presented only in listing. No summaries are planned.

A separate listings will be produced for positive results of drug tests and alcohol breath test more than 0.0 (for purpose of presentation in the statistical report/CSR).

4.12.8. Contraception

Listing containing data regarding contraception used will be prepared for each patient. No summaries are planned.

4.12.9. COVID-19 and tuberculosis

Listing containing information about COVID-19 test 72h prior to Day 1 and results of QuantiFERON-TB GOLD (QFT-G) test will be prepared. No summaries are planned.

Separate listing will contain information from COVID-19 questionnaire.

4.12.10. Patient diary

Information whether subject was trained on how to take medication properly, as well as information on patient diary (dispensing, returning, completing consistently with instruction) will be listed only. No summaries are planned.

4.12.11. Contact checklist

Data from contact checklist collected during the phone call visits will be listed only. No summaries are planned.

4.13. Pharmacokinetic analyses

Analyses will be performed for PS and PSPC populations. Concentration data and calculated PK parameters will be listed for PS population, while data summaries, plots, and inference analyses will be performed in PSPC population. In case PS and PSPC (PS = PSPC) are identical, all analyzes will be performed only in PS analysis set.

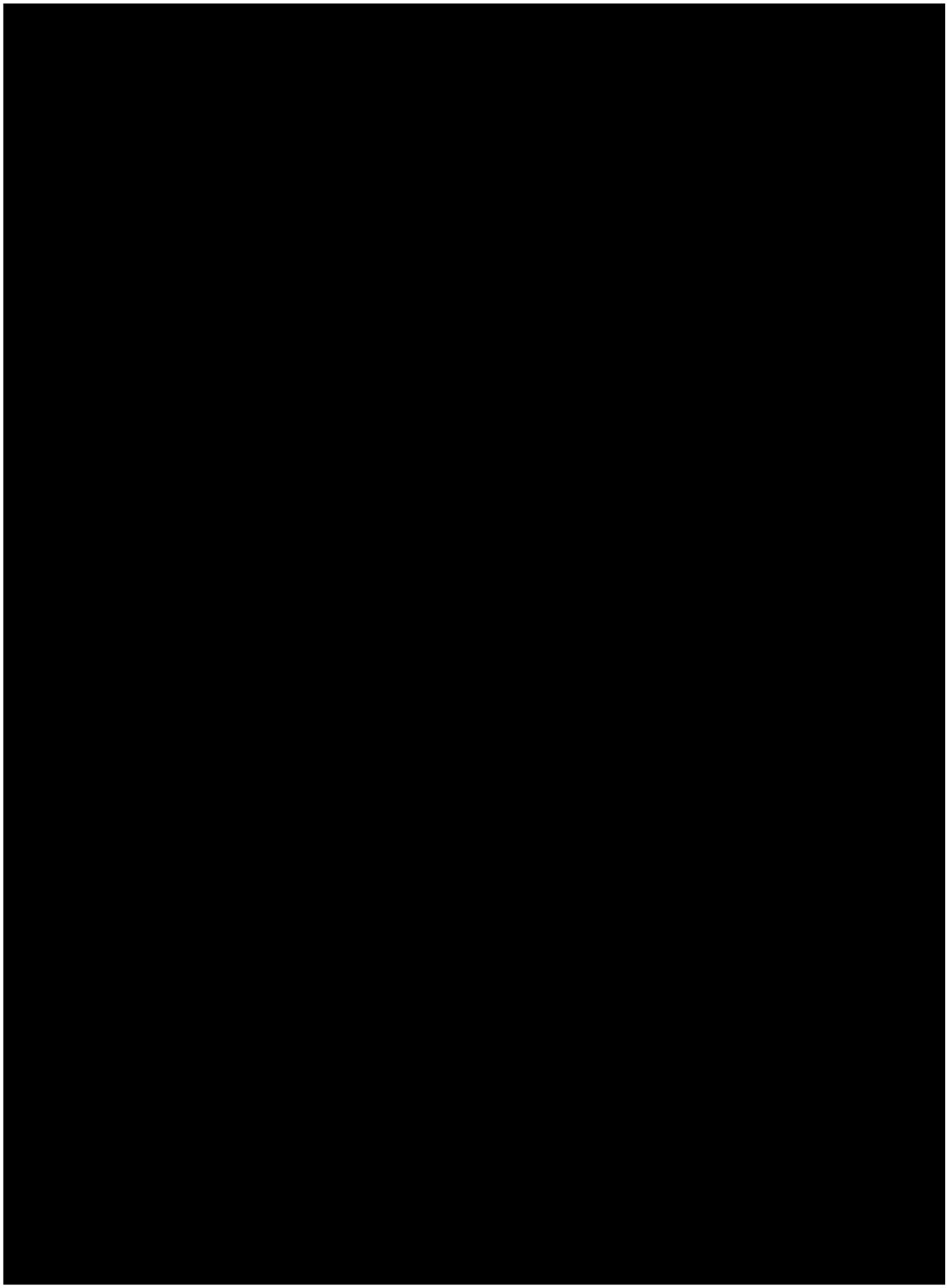
The following pharmacokinetic parameters will be estimated if data permits: $AUC_{(0\text{-}6h)}$, C_{max}, T_{max}, K_{el} and $T_{1/2}$ for CPL409116 and its M3 metabolite, individually for each subject and separately for Days 1, 8, 57, and 85. They will be computed using non-compartmental modelling approach using actual sampling times.

All individual pharmacokinetic parameters described above will be presented in listings and analyzed with descriptive summary statistics including arithmetic mean, geometric mean, median, quantiles Q1 and Q3, standard deviation (SD), coefficient of variation (CV), minimum and maximum. Analyses will be performed in subgroups by dose treatment arm.

Plasma concentration/time curves will be presented for CPL409116 and M3 in linear and log-linear scale. Curves will be presented separately for Dyas 1, 8, 57 and 85 for:

- individual subjects (including additional log-linear scale plot showing points used for Kel calculation) (PS population),
- arithmetic mean ± SD within dose cohort, by dose cohort, in linear scale (PSPC population),
- arithmetic mean within dose cohort, by dose cohort, in log-linear scale (PSPC population),

- overlapping individual curves (with mean curve in different color) for each dose cohort, in linear and log-linear scale (PSPC population).



4.15. Exploratory analyses of pharmacokinetic data

An exploratory PK analysis, not described in the clinical study protocol, will be performed if data permits for both CPL409116 and M3 individually for each subject (and separately for Days 1, 8, 57, and 85, if applicable):

- $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ on Day 85
- %extrapolated AUC on Day 85
- metabolite-to-parent ratio of C_{max} and $AUC_{(0-6h)}$ – based on molar concentrations
- accumulation calculated as $AUC_{(0-6h)}$ ratios Day 8/Day 1, Day 57/Day 1 and Day 85/Day 1
- accumulation calculated as for C_{max} ratios Day 8/Day 1, Day 57/Day 1 and Day 85/Day 1
- linearity of dose-normalized C_{max} and $AUC_{(0-6h)}$
- evaluation of changes in T_{max} (median and range, individual differences) between doses and days of study
- evaluation of changes in $T_{1/2}$ (mean ± SD) on Day 85 between doses
- evaluation of changes in CL/F (mean ± SD) on Day 85 between doses
- evaluation of changes in Vz/F (mean ± SD) on Day 85 between doses
- $C_{max,ss}$ on Days 8, 57 and 85
- $C_{min,ss}$ on Days 8, 29, 57 and 85
- evaluation of steady-state basing on C_{trough} on Days 8, 29, 57 and 85
- evaluation of intra-subject variability in PK between days 8, 57 and 85
- fluctuation on Day 85
- swing on Days 8, 57 and 85.

Additionally to the PK analyses planned in the study protocol, individual ratios of C_{max}, $AUC_{(0-6h)}$, and $AUC_{(0-inf)}$ and differences of T_{max}, between CPL409116 and its metabolite M3 will be calculated and listed. Results of assessment of pharmacokinetics will be compared between CPL409116 and its metabolite M3, i.e. descriptive statistics for individual ratios of C_{max}, $AUC_{(0-6h)}$, and $AUC_{(0-inf)}$ and differences of T_{max}, between CPL409116 and its metabolite M3 will be reported, by dose cohort. To compare results between cohorts, point estimates with 90% confidence intervals for the geometric means ratios between each dose and the middle dose will calculated based on the ANOVA model for individual CPL409116 and its metabolite M3 ratios for each of the above PK parameters (except differences in T_{max}) with fixed effects for dose, separately for Days 1, 8, 57, and 85 of the study. Dose effect on ratio of CPL409116 and its metabolite M3 PK parameters values will be considered neglectable if the calculated 90% confidence interval for the geometric means ratio will completely within the range of 80.00-125.00%. However, due to the small planned sample size, power of the above analysis will be small and results should be interpreted with caution. Differences in T_{max} will be compared between dose cohorts based on the pairwise comparisons using Mann-Whitney test with Bonferroni correction for multiple comparisons.

Assessment of time to steady-state will be performed using descriptive methods and examination of the descriptive statistics and plots of pre-dose and 2.5 hour post-dose concentrations on Days 1-85. No formal statistical methods of estimation of time to steady-state will be applied. Box-plots for plasma concentration of CPL409116 and its metabolite M3 vs. Day (for Days 1, 8, 29, 57 and 85) will be presented for pre-dose (and 12 h sample for Day 85) and 2.5 h after administration concentrations.

To assess proportionality/linearity of relationship between CPL409116 dose and PK parameters following methods will be applied:

- Plots of mean (±SD) PK parameter value versus CPL409116 dose + scatterplot of calculated PK parameters values versus CPL409116 dose, by day of the study, for all calculated PK parameters will be presented.
- Dose-normalized values of C_{max}, $AUC_{(0\text{-}inf)}$, and $AUC_{(0\text{-}6h)}$ will be calculated (i.e. PK parameter value will be divided by the corresponding dose) and summarized using descriptive methods by dose treatment arm and study day 1, 8, 57, and 85.
- The log-transformed dose-normalized parameters C_{max}, $AUC_{(0\text{-}inf)}$, and $AUC_{(0\text{-}6h)}$ and log-transformed parameters $T_{1/2}$, CL/F, and V_z/F will be analyzed using ANOVA with fixed effects for CPL409116 dose, subject and (if applicable) day 1, 8, 57, and 85 of the study. The least square means will be calculated together with 95% CIs. Estimates of the pairwise geometric means ratios between each dose and the middle dose will be calculated together with 90% confidence intervals. CPL409116 dose effect on CPL409116 PK parameters values will be considered neglectable if the calculated 90% confidence interval for the geometric means ratio will be completely within the range of 80.00-125.00%. However, due to the small planned sample size, power of the above analysis will be small and results should be interpreted with caution.
- PK parameter t_{max} will be compared between doses based on the pairwise comparisons using Mann-Whitney test with Bonferroni correction for multiple comparisons, separately for each of days 1, 8, 57, and 85 of the study.
- Assessment of fit of linear model for log-transformed PK parameter (C_{max}, $AUC_{(0\text{-}inf)}$, and $AUC_{(0\text{-}6h)}$) value versus log-transformed CPL409116 dose, separately for day 1, 8, 57, and 85 of the study - the mean slope of the log-transformed parameters against log-dose will be estimated and the corresponding 90% CIs will be constructed; dose-proportionality will be concluded if the slope will not be different from unity.

Additionally intra-subject variability for C_{max}, $AUC_{(0\text{-}inf)}$, and $AUC_{(0\text{-}6h)}$ will be estimated based on the results of analysis of variance model with fixed effects for CPL409116 dose, subject and days 8, 57, and 85 of the study.

Exploratory PK analysis results will be presented in the separate part of pharmacokinetic report. The latter one will be an attachment to the Clinical Study Report. Additional PK parameters, not listed above, may be determined where appropriate.

[redacted]

4.17. Exposure and drug adherence

Exposure and extent of exposure as well as data on drug adherence/compliance will be presented in tabular form with descriptive statistics calculated as described in section 4.2.6.

4.18. Additional analyses

After conclusion of main analyses, additional statistical analysis will be performed. Details of these analyses are beyond the scope of this document but a broad scope is described below.

Primary and secondary endpoints will be analyzed for subgroups based on two additional age categories: 18-37 vs 38-56 years old.

As part of additional analysis several endpoints will be considered:

- Change from Baseline in Disease Activity Score DAS28-ESR at Week 12
- Proportion of subjects based on category of response in change of DAS28-CRP score on week 12 (see section 4.2.8)

- Relationship between DAS28-CRP remission and ACR criteria.

Primary and secondary endpoints will be also analyzed in context of RA duration (<5 years vs. ≥5 years).

All additional analysis will be performed on ITT population without imputation. If results are scientifically encouraging, PP and ITT with imputations will be also used to generate analyses.

5. Software and statistical programming

R programming will be performed according to Biostat standards as defined in PS11/2018 SOP "Data analysis" and related work instructions. The statistical analysis will be performed using the R statistical software package (Version 4.0.3 or later). Calculation of pharmacokinetic parameters will be performed in Phoenix WinNonlin 8.4 or later, except C_{trough}, accumulation ratio for $AUC_{(0\text{-}6h)}$, and accumulation ratio for C_{max}. PK parameters C_{trough}, accumulation ratio for AUC_{tau}, and accumulation ratio for C_{max} calculations and all other than PK parameters calculation analyzes will be performed using R statistical software package (Version 4.1.3 or later), based on the results obtained from the PK parameters calculations performed using WinNonlin or raw data on analyte concentrations. Pharmacodynamic analyses will be performed in R statistical software package (Version 4.1.3 or later).

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