Clinical Study Protocol

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

Sponsor:	Celon Pharma S.A. Ogrodowa 2A Str. 05-092 Łomianki / Kiełpin Poland
Sponsor Study Number:	03JAK2021
EudraCT Number:	2021-006146-12
IMP Name:	PG24
Development Phase:	Phase II
Version (Date) of Final Protocol:	3.0, 20.12.2022

This clinical study will be conducted in accordance with the International Council for Harmonization Tripartite Guideline for Good Clinical Practice (GCP) E6(R2), the protocol and with other applicable regulatory requirements.

Confidentiality Statement

This document contains confidential information of Celon Pharma S.A. Do not copy or distribute without written permission from the Sponsor.

SIGNATURE PAGE

Declaration of Sponsor

I have read and understood the protocol version 3.0, dated 20.12.2022, specified below, and agree on the contents.

Protocol Title: 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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice (GCP) applicable to this clinical study.

Sponsor's Signatory

[redacted]

SIGNATURE PAGE

Declaration of the Investigator

Protocol Title: 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.

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current risk and benefit evaluation of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

I have read all pages of this clinical study protocol, version 3.0, dated 20.12.2022 and confirm that it contains all the information required to conduct this study. I agree to conduct the study as detailed in the protocol and comply with all the terms and conditions set out therein. I confirm that I am to conduct the study in accordance with the provisions of the Declaration of Helsinki. I will also ensure that Investigator(s) and other relevant members of my staff have access to copies of this protocol and the Declaration of Helsinki to enable them to work in accordance with the provisions of the documents and standard operating procedures (SOP's) of designated CRO company. Furthermore, the current International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (ICH-GCP), and local regulations are to be followed.

I acknowledge that all data included in the clinical study protocol are confidential. Copying, disclosing and publishing without the assent of Sponsor is prohibited.

Investigator's Signatory

SIGNATURE PAGE

Declaration of Statistician

I have read and understood the protocol version 3.0, dated 20.12.2022, specified below, and agree on the contents.

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I acknowledge that all data included in the clinical study protocol are confidential. Copying, disclosing and publishing without the assent of Sponsor is prohibited.

Statistician's Signatory

[redacted]

SUMMARY LIST OF CHANGES

Protocol v 3.0 dated 20.12.2022	
Applicable Section Page	**Description of Change(s)**
Whole document	Minor editorial changes including formatting, spelling and wording were implemented trough document in order to clarify and unify the protocol.
List of Study Staff	[redacted]
1.1 Protocol Synopsis Main Inclusion Criteria	**Before change:** 4. Must have a C-reactive protein (CRP) measurement ≥7 mg/L at screening. **After Change:** 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.

	Rationale: Due to the fluctuation in CRP level in RA patients it is possible to re-test CRP level in order to re-evaluate Patients eligibility criteria on Screening.
1.1 Protocol Synopsis Main Exclusion Criteria	**Before change:** 33. Current therapy with any disease-modifying antirheumatic drugs (DMARDs) other than MTX. All DMARDs (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. **After change:** 33. Current therapy with any disease-modifying antirheumatic drugs (DMARDs) other than MTX. All DMARDs (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. **Rationale:** Notification was implemented in order to clarify the protocol.
1.1 Protocol Synopsis Main Exclusion Criteria	**Before change:** 36. Previous use of biologic agent other than tocilizumab or TNF-alpha inhibitor. Previous use of one (and only one) biologic agent (tocilizumab or TNF-alpha inhibitor) is allowed if administered for less than 3 months or ceased because of other than lack of effectiveness causes. **After change:** 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. **Rationale:** Criterion was re-evaluated in order to precise patient population regard to previous use of biologic agent.
1.1 Protocol Synopsis Blood samples collection	**Before change:** • Rheumatoid Factor (RF) are to be collected during the Screening, at Baseline/ Day 1 (Visit 2), Week 8 (Day 57), Week 12 (Day 85) and in case of early withdrawal; **After change:** • Rheumatoid Factor (RF) are to be collected during the Screening, at Baseline/ Day 1 (Visit 2), Week 1 (Day 8), Week 4 (Day 29) Week 8 (Day 57), Week 12 (Day 85), on Day 99 and 113 during the Follow- up period and in case of early withdrawal; **Before change:** • C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) are to be tested during the Screening, Baseline/ Day 1, Week 1, Week 4, Week 8, Week 12, Week 16 and in case of early withdrawal; **After Change:** • C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) are to be tested during the Screening, Baseline/ Day 1, Week 1, Week 4, Week 8, Week 12, Week 14 and Week 16 and in case of early withdrawal; **Before change:**

	• Anti CCP Antibodies (ACPA) are to be collected during the Screening, at Baseline/ Day1, Week 12, Week 16 and in case of early withdrawal. **After change:** • Anti CCP Antibodies (ACPA) are to be collected during the Screening, at Baseline/ Day1, Week 4 (Day 29) Week 8 (Day 57), Week 12 (Day 85), Day 113 and in case of early withdrawal. **Before change:** Fasting lipid profile: fasting total cholesterol, LDL, HDL, triglycerides will be assessed at Screening; Day1/ baseline; Week 4; Week 12 and Week 16 (samples must be collected after a minimum 6-hour fasting). **After change:** Fasting lipid profile: fasting total cholesterol, LDL, HDL, triglycerides will be assessed at Screening, at Baseline/ Day1, Week 1 (Day 8), Week 4 (Day 29) Week 8 (Day 57), Week 12 (Day 85), on Day 99 and 113 during the Follow- up period and in case of early withdrawal (samples must be collected after a minimum 6-hour fasting). **Rationale:** Number of blood donations for laboratory assessments were increased trough the study in order to evaluate study objectives
Table 1. Study schedule and assessment.	**<u>Visit window</u>** **Before change:** Screening: Days -28 to 0 Treatment period (Week 0 – 12): □2 Days based on Week 0/Day 1 visit Follow up: □2 Days based on Week 0/Day 1 visit End of Study: □2 Days based on Week 0/Day 1 visit **After change:** Screening: Days -28 to 0 Treatment period (Week 0 – 10): □2 Days based on Week 0/Day 1 visit Treatment period (Week 12): N/A Follow up: □2 Days based on Week 0/Day 1 visit End of Study: □2 Days based on Week 0/Day 1 visit **Rationale**: Notification was implemented in order to clarify and precise the protocol **<u>Rheumatoid Factor (RF)</u>** **Before change:** Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 57, Day 85; Early Withdrawal **After change:** Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 8, Day 29, Day 57, Day 85; Follow UP: Day 99 End of study: Day 113 Early Withdrawal **<u>C-Reactive Protein (CRP)</u>** **Before change:** Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 8, Day 29, Day 57, Day 85; End of study: Day 113 Early Withdrawal **After change:**

	Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 8, Day 29, Day 57, Day 85; Follow UP: Day 99 End of study: Day 113 Early Withdrawal **<u>Anti CCP Antibodies (ACPA)</u>** **Before change** Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 57, Day 85; Early Withdrawal **After change:** Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 29, Day 57, Day 85; End of study: Day 113 Early Withdrawal **<u>Lipid Profile</u>** **Before change** Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 29 Day 57, Day 85; End of study: Day 113 **After change:** Screening: Days -28 to 0; Treatment Period: Day 1/ Baseline; Day 8, Day 29, Day 57, Day 85; Follow UP: Day 99 End of study: Day 113 Early Withdrawal <u>HBsAg, HBcAb, HBsAb; HBV DNA; HCVAb and HCV RNA</u> **Before change:** Screening: Days-28 to 0; **After change:** Screening: Days-28 to 0; Treatment Period: Week 6 (X) Early Withdrawal (X) **Rationale**: The table was updated with assessments planned to be performed during the study.
Footnotes to Table 1. Study schedule and assessment.	**Before change:** k. RF parameter is to be evaluated at Screening, on Day 1/ baseline; 57, 85 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; 113 and in case of early withdrawal. n. ACPA is to be assessed at Screening; Day 1/ baseline; 85; Day 113 and in case of early withdrawal. o. Fasting lipid profile is to be assessed at Screening, Day1/ baseline, Week 4; Week 12 and Week16 (samples must be collected after a minimum 6-hour fasting), and includes: fasting total cholesterol, LDL, HDL, triglycerides. **After change:** 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. 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. **Rationale:** Text has been modified in order to clarify and unify the protocol.
4.1. Overview	**Before changes:** • Collect blood samples for clinical chemistry (including CRP), coagulology and hematology; • Collect blood sample for ESR testing, RF, ACPA; **After changes:** • Collect blood samples for clinical chemistry, coagulology and hematology; • Collect blood sample for ESR testing, RF, ACPA and CRP; **Before changes:** After randomization and during the **Treatment Period** (...) administered twice a day for 85 consecutive days (Day 1 to Day 85). **After changes:** After randomization and during the **Treatment Period** (...) 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). **Rationale:** Text has been modified in order to clarify and unify the protocol.
5.2 Inclusion Criteria	**Before change:** • Must have a C-reactive protein (CRP) measurement ≥7 mg/L at screening. **After change:** • 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. **Rationale:** Text has been modified in order to clarify and unify the protocol.
5.3 Exclusion Criteria **And** **5.6 Prohibited medications:**	**Before change:** • Current therapy with any disease-modifying antirheumatic drug (DMARD) other than MTX. All DMARDs (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. **After change:** • Current therapy with any disease-modifying antirheumatic drug (DMARD) other than

<table>
<tr><td></td><td>MTX. All DMARDs (except for MTX) must be ceased before Day 1/ baseline, as follows:
(…)
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.

Before change:
• Previous use of biologic agent other than tocilizumab or TNF-alpha inhibitor. Previous use of one (and only one) biologic agent (tocilizumab or TNF-alpha inhibitor) is allowed if administered for less than 3 months or ceased because of other than lack of effectiveness causes.

After change:
• 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.

Rationale: Text has been modified in order to clarify and unify the protocol</td></tr>
<tr><td>Table 6. Clinical laboratory assessment</td><td>Before change:
<table><tr><th colspan="2">Clinical Chemistry</th></tr><tr><td>Alanine aminotransferase (ALT)</td><td>Lactate dehydrogenase (LDH)</td></tr><tr><td>Albumin</td><td>LDL</td></tr><tr><td>Alkaline phosphatase (ALP)</td><td>Phosphorus</td></tr><tr><td>Aspartate aminotransferase (AST)</td><td>Potassium</td></tr><tr><td>Blood urea nitrogen (BUN)</td><td>Sodium</td></tr><tr><td>Calcium</td><td>Total bilirubin</td></tr><tr><td>Chloride</td><td>Total cholesterol</td></tr><tr><td>C-Reactive Protein and CRP</td><td>Total protein</td></tr><tr><td>Creatinine</td><td>Triglycerides</td></tr><tr><td>Creatine kinase (CK)</td><td>Uric acid</td></tr><tr><td>Gamma glutamyl transferase (GGT)</td><td></td></tr><tr><td>Glucose</td><td></td></tr><tr><td>HDL</td><td></td></tr><tr><th colspan="2">Other</th></tr><tr><td colspan="2">Anti CCP Antibodies (ACPA)</td></tr><tr><td colspan="2">Rheumatoid Factor (RF)</td></tr><tr><td colspan="2">Erythrocyte Sedimentation Rate (ESR)</td></tr></table>
After change:
<table><tr><th colspan="2">Clinical Chemistry</th></tr><tr><td>Alanine aminotransferase (ALT)</td><td>Gamma glutamyl transferase (GGT)</td></tr><tr><td>Albumin</td><td>Glucose</td></tr><tr><td>Alkaline phosphatase (ALP)</td><td>Lactate dehydrogenase (LDH)</td></tr><tr><td>Aspartate aminotransferase (AST)</td><td>Phosphorus</td></tr><tr><td>Blood urea nitrogen (BUN)</td><td>Potassium</td></tr><tr><td>Calcium</td><td>Sodium</td></tr><tr><td>Chloride</td><td>Total bilirubin</td></tr><tr><td>Creatinine</td><td>Total protein</td></tr><tr><td>Creatine kinase (CK)</td><td>Uric acid</td></tr><tr><th colspan="2">Other</th></tr><tr><td colspan="2">Anti CCP Antibodies (ACPA)
Rheumatoid Factor (RF)
Erythrocyte Sedimentation Rate (ESR)</td></tr></table></td></tr>
</table>

	C Reactive Protein and CRP **Lipid profile** HDL LDL Total cholesterol Triglycerides **Rationale:** The table was updated and reorganized in order to clarify and unify the protocol.
[redacted]	
9.1 Screening	**Before change:** • Collect blood samples for clinical chemistry including CRP* * CRP must be assessed two times at Screening, the first time up to 72h before Day1/baseline (for evaluation of DAS28-CRP) and the second time within the 72-hour period before Day1/baseline to use a measurement result for DAS28-CRP evaluation on Day1/ baseline. • Collect blood sample for ESR testing, RF, ACPA; **After changes:** •Collect blood samples for clinical chemistry, coagulology and hematology; •Collect blood sample for ESR testing, RF, ACPA, CRP*; * CRP must be assessed two times at Screening, the first time up to 72h before Day1/baseline (for evaluation of DAS28-CRP) and the second time within the 72-hour period before Day1/baseline to use a measurement result for DAS28-CRP evaluation on Day1/ baseline. 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; **Rationale:** Text was added in order to precise the protocol
9.2 Treatment period	**Before change:** 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, Day 85- only one dose of CPL409116 in the morning). (…) In case of other, prolonged deviations consultations with the Sponsor are required. **After change:** 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, Day 85- only one dose of CPL409116 in the morning). (…) Visit Window for Patient ambulatory visit **is not applicable for Day 85**, due to the end of Treatment Period and endpoints assessments. In case of other, prolonged deviations consultations with the Sponsor are required. **Visit 2 Baseline Da1/Week 0** **Before change:** -Collect blood samples for chemistry (including CRP* 72h before visit), haematology and the coagulation profile laboratory assessments; -Collect blood samples for RF, ACPA **After change:**

	-Collect blood samples for chemistry, haematology and the coagulation profile laboratory assessments; -Collect blood samples for RF, ACPA and CRP (including testing 72h before visit) **Visit 3, Day 8/Week 1** **Procedures that are to be performed on Visit 3, include:** **Before change:** • Collect blood samples for chemistry (including CRP), haematology and the coagulation profile laboratory assessments; **After change:** • Collect blood samples for chemistry, haematology and the coagulation profile laboratory assessments; • Collect blood sample for CRP, RF, ESR and lipid profile assessment **Visit 4, Day 29/Week 4; Visit 6, Day 57/Week 8 and Visit 8, Day 85/Week 12** **Procedures that will be performed pre-dose:** **Before change** • Collect blood samples for chemistry (including CRP), haematology and the coagulation profile laboratory assessments; **After change:** • Collect blood samples for chemistry, coagulation and haematology laboratory assessments; • Collect blood sample for ACPA, CRP, RF, ESR and lipid profile assessment **Visit 8/ Day 85/Week 12** **Following text was added:** Morning dose is the last dose of IMP taken by subject during this study. **Follow-Up/Visit 9, Day 99/Week 14** **Before change** • Collect blood sample for ESR assessment **After change:** • Collect blood sample for CRP, RF, ESR and lipid profile assessment **Follow-Up/Visit 10, Day 113/ Week 16** **Before change:** • Collect blood samples for chemistry (including CRP), haematology and coagulology laboratory assessments; • Collect blood sample for ESR assessment; • Collect blood sample for ACPA assessment; • Collect blood samples for lipid profile assessment; **After change:** • Collect blood samples for chemistry, haematology and coagulology laboratory assessments; • Collect blood sample for ACPA, CRP, RF, ESR and lipid profile assessment;

	Early withdrawal **Before change:** • Collect blood samples for chemistry (including CRP), haematology and coagulology laboratory assessments; • Collect blood samples for RF, ACPA, **After change:** • Collect blood samples for chemistry, haematology and coagulology laboratory assessments; • Collect blood samples for RF, ACPA, CRP **Rationale:** Text was implemented in order to clarify and precise the protocol

Protocol v 2.0 dated 01.03.2022	
Applicable Section Page	**Description of Change(s)**
List of Study Staff	[redacted]
List of Abbreviations and Definitions of Terms; **1.PROTOCOL SUMMARY** **1.1. Protocol Synopsis** **Secondary Patient Reported Outcome Endpoints** **8. STUDY ASSESSMENTS AND PROCEDURES**	**Before changes:** SF-36 v.2 (Acute) **After changes:** SF-36 RAND **Rationale:** SF-36 v.2 (Acute)- accessible with a software only which is not compatible with Sponsor's eCRF. The scale had to be changed to SF-36 RAND. SF-36 RAND uses the same questions as SF-36 v.2 (Acute) to assess patient's condition. All clinical scales will be submitted with the Protocol v. 2.0 in The Ethics Committee and The Regulatory Office.

1.PROTOCOL SUMMARY **1.1.Protocol Synopsis** **Main Inclusion Criteria**	**Before changes:** 9. A woman must be either: a. Not of childbearing potential: - postmenopausal (>45 years of age with amenorrhea for at least 12 months, without using exogenous hormonal contraception and with FSH ≥ 40 IU/L); **After changes:** 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); **Rationale:** After the age of 60 years, the FSH concentration tends to decrease gradually and may drop below 40 IU/L. In order to avoid applying contraception in women ≥60 years of age FSH is to be verified only up to the age of 60 to confirm postmenopausal status.
1.3. Schedule of Assessments, Time Points and Window Allowance **Table 1. Study schedule and assessment.** **Footnotes to Table 1.**	**Before changes:** **After changes:** Supplementing the table with missing medical procedures described in the text of the previous Protocol version 1.0 and information about the Patient's card was added. • Physician's Global Assessment of Arthritis (PhGA) • HAQ-DI • DAS28-CRP • SF-36 RAND • **"**Dispensing of Patient's card" item was added. It is to be dispensed on Day 1/ baseline In Footnotes additional description on the basis of primary and secondary endpoints was added: 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. **Rationale:** Changes for greater accuracy and to avoid misunderstandings in Investigators and medical staff.

1.3. Schedule of Assessments, Time Points and Window Allowance **Table 1. Study schedule and assessment.** **Footnotes to Table 1, point l**	**Before changes:** ESR will be performed using the Westergen method 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. **After changes:** 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 **Rationale:** Changes made based on comments from laboratories performing safety measurements – ESR measurement is in general performed automatically in different devices.
4. STUDY DESIGN **4.1. Overview** **9.STUDY SCHEDULE** **9.1 Screening**	**Before changes:** **NOTE:** 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 **After changes:** **NOTE:** 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. **Rationale:** The randomised code will be generated after the negative result of COVID-19 test received at Screening. It will take place <72 hours before Day1/ baseline. Some of inclusion and exclusion criteria will be finally evaluated on Day1/ baseline according to the Protocol. Both, randomisation and code generation have to take place before Day1/ baseline because it requires time to prepare kits of Investigational Medicinal Products and placebo by a pharmacist at site for a patient.
4. STUDY DESIGN **4.1. Overview** **9. STUDY SCHEDULE** **9.2.Treatment Period**	**Before changes:** At every outpatient visit appropriate number of CPL409116/ placebo tablets and a new diary will be dispensed whereas the previous diary (completed) is to be attached to the documentation of the study. The last diary is to be dispensed on Day 57 (Week 8) and collected on Day 85 (Week 12).

	After changes: 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). **Rationale:** Implemented in order to clarify. The Patient's diary is to be consisted of 4 parts for 4 stages of the trial. Each part is to be dispensed during an appropriate ambulatory visit taking place before the respective stage.
6.INVESTIGATIONAL MEDICINAL PRODUCT **6.6. Dosing**	**Before changes:** Patients will be given a subject diary and provided with instructions on the completion of the diary. The diary will be filled out by the Investigator during ambulatory visits in the morning. **After changes:** Patients will be given a subject diary and provided with instructions on the completion of the diary. The diary won't be filled during Patient's visit at Site. The data during ambulatory visits will be recorded in source documentation. **Rationale:** The data will be entered in the source documentation at an outpatient visit, filling in the diary by Investigator is to be unnecessary.
6.INVESTIGATIONAL MEDICINAL PRODUCT **6.6. Dosing** **6.7.Compliance and IMP Accountability**	**Before changes:** Pharmacist **After changes:** Pharmacist *or delegated person* **Rationale:** Either Pharmacist or delegated person will be responsible for the turnover of IMP/ placebo at Site. The change implemented in order to improve the operational organisation of clinical sites.
8.STUDY ASSESSMENTS AND PROCEDURES **8.2. Clinical laboratory assessments, medical procedures** **Vital Signs**	**Before changes:** Blood pressure will be measured in the subject's dominant arm and recorded to the nearest mmHg. The same arm will be used throughout the study. All blood pressure in this study will be measured with the subject in the sitting position after resting for at least 5 minutes. **After changes:**

	Blood pressure will be measured in the subject's dominant arm and recorded to the nearest mmHg. The same arm will be used throughout the study. All blood pressure in this study will be measured with the subject in the sitting *or lying* position after resting for at least 5 minutes. **Rationale:** for the greater discretion of Investigators.
8.STUDY ASSESSMENTS AND PROCEDURES **8.3.Pharmacokinetics and Pharmacodynamics Variables**	**Before changes:** PK samples on Day 1/ baseline Pre-dose 0.0: ≤ 5 min before CPL409116 administration in the morning **After changes:** PK samples on Day 1/ baseline Pre-dose 0.0: ≤ 30 min before CPL409116 administration in the morning **Rationale:** The change implemented in order to improve the operational activity on Day 1/ baseline at clinical sites.
8. STUDY ASSESSMENTS **8.4. Efficacy**	**Before changes:** Patient's Global Assessment (PtGA) of Arthritis. Question: Considering all the ways your arthritis affects you, how are you feeling today? **After changes:** Patient's Global Assessment (PtGA) of Arthritis. Question: Considering all the ways in which your rheumatoid arthritis affected you, how do you feel about your arthritis today? **Rationale:** The question after changes consistent with a question available in Patient's Global Assessment (PtGA) of Arthritis scale which is to be used in that clinical trial.
8. STUDY ASSESSMENTS **8.4. Efficacy** **Disease Activity Score (DAS) Assessments**	**Before changes:** The components of the DAS 28 arthritis assessment include: •Tender/Painful Joint Count (28); •Swollen Joint Count (28); •CRP; •Patient's Global Assessment of Arthritis **After changes:** The components of the DAS 28 arthritis assessment include: •Tender/Painful Joint Count (28);

	•Swollen Joint Count (28); •CRP; •VAS disease activity (0-100mm). **Rationale:** In order to clarify.
9. STUDY SCHEDULE **9.1 Screening**	**After changes:** *CRP should be assessed two times at Screening, the first time up to 72h before Day1/baseline (for evaluation of DAS28-CRP) and the second time within the 72-hour period before Day1/baseline to use a measurement result for DAS28-CRP evaluation on Day1/ baseline. **Rationale:** Information was added to clarify which a CRP result will be used to evaluate DAS28-CRP on Day1/ baseline
9. STUDY SCHEDULE? **9.2.Treatment Period** **Visit 2 Baseline Day 1/ Week 0**	**Before changes:** -Collect blood samples for chemistry (including CRP), haematology and the coagulation profile laboratory assessments; **After changes:** -Collect blood samples for chemistry (including CRP* 72h before visit), haematology and the coagulation profile laboratory assessments; **Rationale:** DAS28-CRP must be assessed on Day1/ baseline. CRP is needed to evaluate DAS28-CRP however measurement of CRP on Day1/ baseline before IMP administration in the morning will be impossible therefore CRP from the 72- hour period before Day1/ baseline will be used to assess DAS28-CRP on Day1/baseline.

LIST OF STUDY STAFF

Sponsor	[redacted]
Sponsor's representative	
Sponsor's Project Management	
CRO Project Management	
Study Coordinator	
Serious Adverse Event Reporting	

Medical Monitor	[redacted]
Bioanalytical Laboratory	
Exploratory Central Laboratory	
Biostatistics	
Funding	

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACPA	Anti-citrullinated protein antibody
ACR/EULAR	American College of Rheumatology/ European League Against Rheumatism
ACR 20 (50/70/90)	20%(50/70/90%) improvement in American College of Rheumatology criteria
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC0-24	Area under the concentration-time curve from time zero to 24 hours
AUC0-48	Area under the concentration-time curve from time zero to 48 hours
AUC0-inf	Area under the concentration-time curve from pre-dose (time 0) extrapolated to infinite time
BCG	Bacille Calmette- Guérin (vaccine)
bDMARDs	Biologic disease-modifying antirheumatic drugs
BID	Lat. bis in die , two times a day
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BT	Body temperature
BUN	Blood urea nitrogen

BW	Body weight
CCP	Anti-cyclic citrullinated peptide
CFP-10	Culture Filtrate Protein-10
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CoA	Certificates of analysis
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
COX-2 inhibitors	Cyclooxygenase-2 inhibitors
CRO	Contract research organization
CRP	C-Reactive Protein
csDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score 28 C - reactive protein
DLT	Dose limiting observations
DMARDs	Disease-modifying antirheumatic drugs
DMP	Data Management Plan
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate

ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency (EU)
EOS	End of Study
ESAT-6	Early Secretory Antigenic Target-6
ESR	Erythrocyte Sedimentation Rate
EW	Early Withdrawal
FACIT-F	Functional Assessment of Chronic Illness Therapy Fatigue
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GCs	Glucocorticoids
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma glutamyl trasferase
GLP	Good Laboratory Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
Hb	Hemoglobin
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B DNA
HCT	Hematocrit

HCV	Hepatitis C virus
HCV RNA	Hepatitis C RNA
HCVAb	Anti-HCV Antibody
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HR	Heart rate
IC50	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IGRA	Interferon-gamma release assay
ILD	Interstitial Lung Disease
IMP	Investigational medicinal product
INF-γ	Interferon-gamma
INR	International Normalized Ratio
IP	Investigational product
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	Intent to Treat Set
IUD	Intrauterine device
IUS	Intrauterine hormone-relasing system (contraception)
[redacted]	
Kel	Elimination rate constant

LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCS	Mental Component Score
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MRI	Magnetic Resonance Imaging
MRMM	Mixed-Effect Repeated Measures Model
MTD	Maximum Tolerated Dose
MTX	Methotrexate
[redacted]	
NOAEL	No-observed-adverse-effect-level
NSAIDs	Nonsteroidal anti-inflammatory drugs
NTM	Nontuberculous Mycobacteria
OECD	Organization for Economic Co-operation and Development
OPRR	Office for Protection from Research Risks
OTC	Over-the-counter
PAAP	Patient's Assessment of Arthritis Pain
PAH	Pulmonary Arterial Hypertension
PCS	Physical Component Score

PhGA	Physician's Global Assessment of Arthritis
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol Set
PPD	Purified Protein Derivative
PS	Pharmacokinetic Analysis Set
PSPC	Pharmacokinetic Set for parameter calculation
PT	Prothrombin time
PtGA	Patient's Global Assessment of Arthritis
QD	Once daily
QFT	QuantiFERON Test
QFT-G	QuantiFERON-TB GOLD Test
RA	Rheumatoid Arthritis
RBC	Red blood cell
RF	Rheumatoid Factor
ROCK	Rho-associated kinase
RR	Respiratory rate
RT-PCR	Real-time Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SF-36 RAND	36-item generic health status measure (Health Survey)

SJC	Swollen Joint Count
SMP	Safety Management Plan
SOC	System organ class
SOP	Standard operating procedure
SS	Safety Analysis Set
STAT	Signal Transducer and Activator of Transcription
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
TB	Tuberculosis
TJC	Tender Joint Count
T_{max}	Time of maximum plasma concentration
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor alpha
Tyk2	Tyrosine kinase 2
ULN	Upper limit of normal
VAS	Visual analog scale
VS	Vital signs
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
WONCBP	Women of non-childbearing potential
β-hCG	β-human chorionic gonadotropin

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title	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.
Study Numbers	Sponsor Protocol No.: 03JAK2021
Development Phase	Phase II
Sponsor	Celon Pharma SA
Study Center	This study will be conducted at multiple clinical centers
Study Objectives	**Primary Objective:** **Efficacy:** - to determine the efficacy of CPL409116 at 12 weeks, in subjects with active RA who have had an inadequate response to methotrexate (MTX). **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. [redacted]

Study Design	This is to be 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. Eligible subjects will be randomised into one of the 4 treatment arms and approximately 100 male and female subjects are to be enrolled in the study. Of the 100 patients: • 25 are to be randomised 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 the 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 is to include the screening period, the treatment period and the follow-up period. In the screening period, patients are to undergo screening assessments from Day -28 to Day 0. Rolling admission is to be employed in this study. Patients that fulfil all the inclusion criteria and none of the exclusion criteria will be considered eligible for this study. During the Treatment Period, patients are to be dosed with 60, 120, 240 mg CPL409116 administered twice a day or placebo administered twice a day for 85 consecutive days (Day 1 to Day 85). Ambulatory visits are to take place on Day 1/ Baseline; 8; 29; 57 and 85, whereas on Day 15 (Week 2); Day 22 (Week 3); Day 43 (Week 6) and on Day 71 (Week 10) phone call to patients will be made to monitor potential adverse events and compliance. On Day 85 patients will be hospitalized up to Day 86 in the morning due to blood samples collection in 13 timepoints for PK analysis. Subjects can spend Day 85 night to Day 86 outside of the clinic but it is necessary to return on Day 86 in the morning to donate the last sample of blood 24h (+/5 min) after morning CPL409116 administration on Day 85. The MTX dosage which should be orally or parenterally administered by participants during the study and before the start of the study should be in the range of 15-25 mg/week, which is typical of current Polish practice. MTX must be applied 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.

	All patients will undergo PK sampling during the Treatment Period. Timepoints for blood samples collection are indicated on the basis of results from completed Phase IB clinical trial. [redacted] Investigational product tablets will be administered to the subject in the clinic in the morning of clinic visits and all other dosing will be performed by the subject outside the clinic, at home Within the follow-up period patients are to come to the study centre two times after the last dose of IMP. – in the Week 14 and 16 (Day 99 and 113 respectively); whereas in the Week 13 and 15 (Day 92 and 106 respectively) phone call from the study unit will be made.
Investigational Medicinal Product	**PG242** (with 60 mg CPL409116 as an active substance, API), uncoated tablets **PG242P** (placebo), uncoated tablets
Number of Subjects	Approximately 100 subjects with rheumatoid arthritis meeting all the inclusion and none of the exclusion criteria are to be enrolled and randomised in 4 arms: Arm 1: **25** patients, CPL409116 at a dose of 60 mg BID, Arm 2: **25** patients CPL409116 at a dose of 120 mg BID, Arm 3: **25** patients CPL409116 at a dose of 240 mg BID Arm 4: **25** patients, the arm with placebo
Study Population	Male and female patients with active rheumatoid arthritis who have an inadequate response to methotrexate.
Main Inclusion Criteria	**Inclusion Criteria** Patients eligible for inclusion in this study have to 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. <u>Not of childbearing potential:</u> - 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. <u>Of childbearing potential</u> 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 <u>for 12 weeks</u> 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).
Main Exclusion Criteria	**Exclusion Criteria** Patients eligible for inclusion in this study must **<u>not</u>** fulfill 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 10^9/L (<1500/mm^3); c. Absolute lymphocyte count of <0.75 x 10^9/L (<750/mm^3); d. Absolute white blood cell (WBC) count of < 3.0 x 10^9 /L (<3000/mm^3); e. Hemoglobin <9.0 g/dL (90 g/L); f. Thrombocytopenia, as defined by a platelet count <100 x 10^9/L (< 100 000/mm^3) 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 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 drugs (DMARDs) other than MTX. All DMARDs (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 (at any time): 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.
Criteria for Evaluation	**Efficacy:** *Primary Endpoint:* – Change from Baseline in Disease Activity Score (DAS)28- C Reactive protein (CRP) at Week 12 . **Secondary Endpoints** *Secondary Clinical Efficacy Endpoints:* *Change form Baseline:* 1. Proportion of subjects with DAS28-CRP remission at Weeks 4; 8 ; 12 and 16; 2. American College of Rheumatology (ACR)20, ACR 50, ACR 70, and ACR 90 responder rates (Weeks 4, 8 and 12); 3. Change from Baseline in the Tender/Painful and Swollen Joint Count (Weeks 4, 8 and 12); 4. Change from Baseline in the Physician's Global Assessment (PhGA) of Arthritis (Weeks 4, 8 and 12).

	Secondary Safety Endpoint: 1. 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). *Secondary Patient Reported Outcome Endpoints* 1. 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; 2. Change from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 4, 8, and 12; 3. Change from baseline in the SF-36 RAND 8 Domain scores and Physical Component Score (PCS) and Mental component score (MCS) at Week 12; 4. Change from baseline in the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) total score at Week 12. *Secondary Pharmacokinetic Endpoints:* 1. CPL409116 and metabolite M3 pharmacokinetic variables: AUC(0-6h), Cmax, Tmax, T1/2 (if possible) and Kel (if possible) determined on Day 1, 8, 57 and 85; 2. CPL409116 pharmacokinetic variables: C0h, C2.5h determined on Day 29. [redacted]

	[redacted]
Blood samples collection	**Blood samples for laboratory tests** Blood Chemistry, Hematology, Coagulation are to be collected: • once during the Screening period and next on Day 1/ Baseline, 8, 29, 57, 85 – as a treatment period and on Day 99 and 113 during the Follow-up period. Blood samples to evaluate: • **Rheumatoid Factor (RF)** are to be collected during the Screening, at Baseline/ Day 1 (Visit 2), Week 1 (Day 8), Week 4 (Day 29) Week 8 (Day 57), Week 12 (Day 85), on Day 99 and 113 during the Follow-up period and in case of early withdrawal; • **C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR)** are to be tested during the Screening, Baseline/ Day 1, Week 1, Week 4, Week 8, Week 12, Week 14 and Week 16 and in case of early withdrawal; • **Anti CCP Antibodies (ACPA)** are to be collected during the Screening, at Baseline/ Day1, Week 4 (Day 29) Week 8 (Day 57), Week 12 (Day 85), Day 113 and in case of early withdrawal. Fasting lipid profile: fasting total cholesterol, LDL, HDL, triglycerides will be assessed at Screening, at Baseline/ Day1, Week 1 (Day 8), Week 4 (Day 29) Week 8 (Day 57), Week 12 (Day 85), on Day 99 and 113 during the Follow-up period and in case of early withdrawal (samples must be collected after a minimum 6-hour fasting). QuantiFERON sampling: Test is to be performed at Screening. HBsAg, HbcAb, HBsAb, HBV DNA, HCVAb, HCV RNA; HIV tests are to be performed at Screening. Total blood loss regarding tests listed above in the study is to be approximately **ca 230 mL** per each subject. **PK sampling** Blood samples for PK analysis are to be collected on the following Days: 1/Baseline; 8; 57 (timepoints: pre-dose and 0.5; 1.0; 1.5; 2.0; 2.5; 3.0; 4.0; 6.0h after CPL409116 administration in the morning) and on Day 29 in the following 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; 24h (Day 86) after CPL409116 administration in the morning. Per each sample will be taken **4,5 mL** of blood. Total amount of blood for PK tests during the study is to be equal approx. **189 mL.** [redacted] Total blood loss in this study is to be maximum **466 mL** per each subject.
Statistical Methods	**Statistic Considerations** Following assumptions have been made for the purpose of sample size determination: ▪ CPL409116 molecule study will be based on four parallel study arms (placebo and three increasing doses of CPL409116); ▪ No interim analyses for efficacy are planned; ▪ Subject with active rheumatoid arthritis (Baseline DAS28>3.2) ▪ Study is performed in a multiple clinical sites; ▪ Primary objective is considered: Change from Baseline in Disease Activity Score (DAS)28-C Reactive protein (CRP) (Week 12); ▪ The primary endpoint will be analyzed using a mixed effect repeated measures model (MRMM). However, to estimate sample size a simulation based on ANCOVA model was used. This should be more conservative (i.e. should underestimate statistical power) than MRMM but allows for more robust sample size estimation; ▪ Analyses for each dose will take form of ANCOVA model with Baseline DAS28-CRP, clinical site (up to five sites were considered in simulation) and drug dose (encoded as levels 1-3) as independent variable; ▪ for both endpoints a normal distribution of baseline and final values is assumed; ▪ in the scenario single ANCOVA model will be performed at the end of the study. Study is successful if at least one

	treatment arm is superior to placebo. Eighty four subjects (21 per treatment group) are required to have a 80% chance of detecting, as significant at the 5% level, a mean change in DAS28-CRP of -1.8 provided that change no greater than -1.0 will be observed in placebo group with combined standard deviation of 1.1. With dropout of ~16% - 100 subjects should be recruited, which gives 25 subject in each treatment group.

1.2. Schema overview

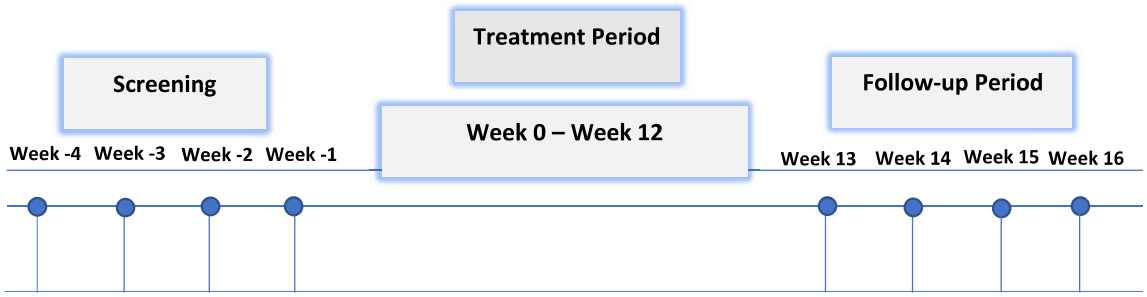


Fig. 1. Schema overview of the study: the Screening, the Treatment Period, the Follow- up Period.

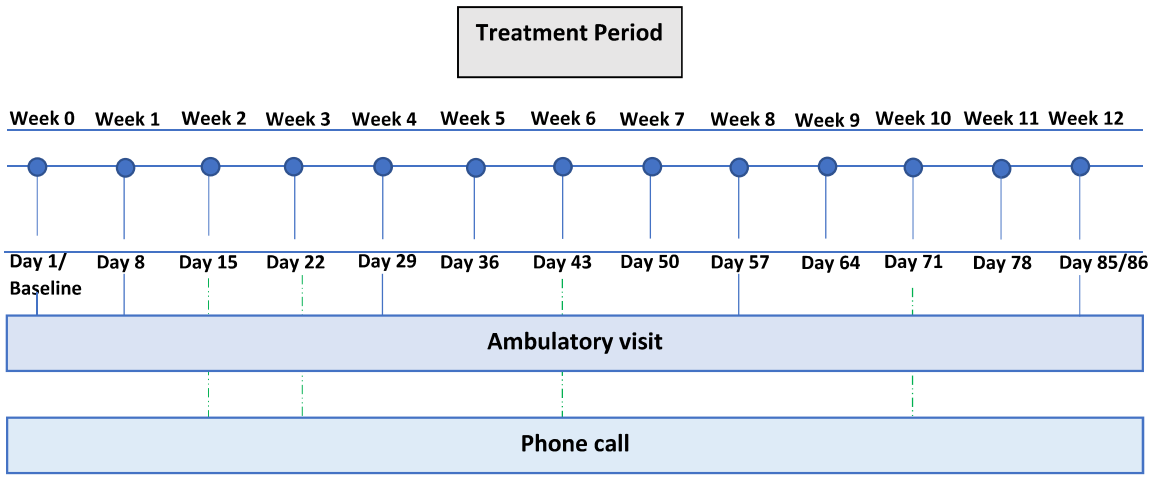


Fig. 2. Schema overview of the treatment period. Ambulatory visits, PK blood samples collection and phone call visits.

1.3. Schedule of Assessments, Time Points and Window Allowance

Study plan for JAK/ ROCK inhibitor- CPL409116, delivered by uncoated tablets in phase II multiple dose study in subjects with rheumatoid arthritis.

The schedule of activities table presents an overview of the protocol visits and medical/ diagnostic procedures. The Principal Investigator may indicate visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations required to protect the well-being of the subject.

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
Targeted Physical Examination [f]			X			X		X			
ECG (12 lead) [g]	X	X	X					X		X	X
Chest X-ray [h]	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		
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										
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

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		
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
[redacted]											
Special laboratory studies/ Blood collection for PK analysis (aa)		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]											
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
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

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		
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									
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 X-ray 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 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. 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 SARS-CoV-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. INTRODUCTION

2.1. Background

Rheumatoid arthritis is a chronic autoimmune connective tissue disease that primarily affects joints and is associated with progressive disability and premature death. RA is a heterogeneous disease, with variable clinical presentation and pathogenic mechanisms involved between individuals with the same formal diagnosis or across different disease stages. The markers of RA are autoantibodies to immunoglobulin G (rheumatoid factor (RF)) and citrullinated proteins (anti-citrullinated protein antibodies (ACPAs)), although some individuals are negative for these autoantibodies (seronegative RA). The disease pathogenesis is complex and involves environmental factors that trigger disease in genetically susceptible individuals. The triggers of disease remain not fully recognized but may include smoking, silica exposure, infectious agents, vitamin D deficiency, obesity and changes in the microbiota. In most patients, the pathogenetic process begins years before clinical onset of RA, although acute onset is also possible. RF and ACPAs, which are generated in immune response against citrullinated or other post-translational modified proteins, are often detected as early as 10 years before the disease onset. In early RA synovial inflammation based on mononuclear cells infiltration is observed. In addition to ACPA other autoantibodies are also detected. While the disease progress the intimal lining of synovium greatly expands, what is associated with increase of IL-1, IL-6 and TNFα production by synovicytes. The second change associated with RA is infiltration of adaptive immune cells to the synovial sublining. Damage to cartilage and bone due to synovial invasion into articular structures is a cardinal sign of RA. Approximately 0.3–1% of people are affected with RA worldwide. Although we cannot yet cure RA, remission is now an achievable goal. However, many patients still cannot attain remission and more work is needed to provide every patient with the benefit of therapeutic success. The current treatment procedure for RA is based on synthetic and biological Disease-Modifying antirheumatic drugs (DMARDs). Conventional synthetic DMARDs, like methotrexate accompanied for a limited period of time with glucocorticoids, are the first choice for RA treatment. For patients who do not obtain sufficient therapeutic effect after conventional synthetic DMARDs treatment targeted synthetic DMADRs (JAK inhibitors belong to this group) and biologic DMRDs are an option.

Cardiovascular disease accounts for the largest proportion of excess mortality in rheumatoid arthritis, accounting for 39.6% of deaths (Sokka et al., 2008). According to literature rheumatoid arthritis was associated with a 48% increased risk of cardiovascular events and a 50% higher incidence of cardiovascular disease related mortality compared with the general population (Aviña-Zubieta et al., 2008). Pulmonary Arterial Hypertension (PAH) is a disease that affects both the heart and lungs, since high pressure in the arteries of the lungs but it has severe consequences for both the heart and the lungs and its incidence is also increased in RA patients. The prevalence rate of PAH in RA patients ranges from 21 % to 27.5 % based on echocardiographic diagnosis (Yang et al., 2013).

One of the most feared clinical manifestations of RA, causes serious morbidity and increased mortality is Interstitial Lung Disease (ILD) which is defined as a progressive fibrotic disease of the lung parenchyma. ILD remains a huge challenge for clinicians up to these days. Firstly, evaluation of respiratory symptoms in patients with RA is challenging because of the many potential causes to be considered, as follows: ILD, chronic obstructive pulmonary disease (COPD), bronchiectasis, respiratory infections following immunosuppressive therapies, drug-induced pulmonary toxicity, and ischemic heart disease. Secondly, there is no available evidence-based therapy for RA-ILD, and immunosuppressants are the mainstay of therapy.

As was mentioned above patients with rheumatoid arthritis typically have circulating autoantibodies, the most common being rheumatoid factor and anti-cyclic citrullinated peptide (CCP). Both types of antibodies have been linked to the development of ILD, particularly when present in high titres. A recent study examined the protein content in tissue samples obtained from lung and synovial biopsies of patients with rheumatoid arthritis, and found identical citrullinated vimentin peptides in both sites thus indicating the link between the two types of disease.

Taking into account fibrotic nature of the changes in the lung parenchyma in patients with Interstitial Lung Disease ongoing studies are exploring the role of antifibrotic therapy in this condition, which may lead to a new treatment approach for subgroups of patients with RA-ILD. Survival in patients with RA has improved in recent years, but patients with RA-associated ILD still have significantly decreased survival compared to patients with RA alone. Previous RA-ILD studies report a median survival of three to ten years. More recent studies tend to show longer survival which may be associated with improved radiological techniques and increased awareness of RA-ILD among clinicians leading to earlier diagnosis (Bendstrup et al, 2019), (Iqbal et al, 2015), (Shaw et al, 2015).

CPL409116 is a novel kinase inhibitor with enhanced selectivity toward Janus family kinases (JAKs) and with an inhibitory activity also towards Rho- associated kinases (ROCK kinases).

A structure of CPL409116 has a few functional groups responsible for the activity and selectivity against JAK kinases. JAK kinases family belongs to non-receptor tyrosine kinases (Ghoreschi K, Laurence A, 2009). Mammals have four members of this family: Jak1, Jak2, Jak3 and Tyrosine kinase 2 (Tyk2). The discovery of cytokines as key drivers of immune-mediated diseases brought an idea to stop its signalling in order to obtain disease remission. JAKs are essential signalling mediators downstream of many proinflammatory cytokines like IL-6, IL-12, IL 15, IL 21, IL-23, granulocyte CSF (G CSF) and IFNs. Upon binding of cytokines to their receptors, JAKs are activated and phosphorylate the receptors, creating docking sites for signalling molecules, especially members of the signal transducer and activator of transcription (STAT) family. Multiple STAT factors have been described as inductors of the expression of many proinflammatory genes and are expressed in the synovial tissue of patients with RA. STAT activation correlates with disease activity in RA, revealing that this signalling pathway is crucial for disease pathogenesis. There is increasing evidence coupling the specific JAK proteins to individual cytokine responses, although there is not yet a comprehensive and detailed description of these mechanisms. Due to its inhibitory effect on cytokine signalling small-molecule inhibitors of JAKs became safe and efficacious options for the treatment of inflammation-driven pathologies such as rheumatoid arthritis (RA) (Gadina et al., 2020) (O'Shea et al., 2015). Rho-associated kinases ROCK1 and ROCK2 are serine/threonine kinases that are downstream targets of the small GTPases RhoA, RhoB, and RhoC. ROCKs are involved in diverse cellular activities including actin cytoskeleton organization, cell adhesion and motility, proliferation and apoptosis, remodeling of the extracellular matrix and smooth muscle cell contraction. Extensive experimental and clinical studies support a critical role for the RhoA/ROCK pathway in the pathogenesis of cardiovascular diseases, in which increased ROCK activity mediates vascular smooth muscle cell hypercontraction, endothelial dysfunction, inflammatory cell recruitment and vascular remodelling. It is therefore not surprising that ROCK activation has been demonstrated in the lungs of humans with IPF and mice in models of this disease. ROCK activity assessed in situ is increased specifically in areas of the lungs developing fibrosis in mice and humans (Zhou et al., 2013) activated fibroblasts isolated from these lungs demonstrate increased ROCK activity compared with quiescent fibroblasts isolated from normal lungs. Activated fibroblasts are central effector cells in pulmonary fibrosis, and ROCK signalling is required for their activation in response to both biochemical and biomechanical signals present in the fibrosis lung. ROCK signalling also appears to be involved in profibrotic responses of epithelial and endothelial cells to tissue injury. Their involvement in the profibrotic responses of multiple cells types suggests that the Rho kinases are focal points in pulmonary fibrosis, through which many upstream signals induce profibrotic downstream responses. ROCK inhibition may therefore be a particularly potent therapeutic strategy for pulmonary fibrosis. Pharmacologic ROCK inhibitors have been shown to prevent the development of

pulmonary fibrosis in mice when administered prior to lung injury, and were more recently shown to reverse already established pulmonary fibrosis (Knipe et al, 2015). Taking the above-mentioned data into account it is highly probable that CPL409116 will be a very potent medication for treatment of autoimmune diseases associated with pulmonary fibrotic changes including RA-ILD or complicated SARS-CoV-2 infections. Moreover, the CPL409116 mode of action based on Rho- associated kinases inhibition can be extremely supportive in patients with RA in whom risk of cardiovascular events is significantly increased (RA was associated with a 48% increased risk of cardiovascular events and a 50% higher incidence of cardiovascular disease related mortality compared with the general population). Generally, according to the literature data cardiovascular disease accounts for the largest proportion of excess mortality in RA, accounting for 39.6% of deaths (Sokka et al., 2008) or (Aviña-Zubieta et al., 2008).

2.2. Summary of Findings from Non-clinical Studies with Potential Clinical Relevance

Toxicology

The toxicology package required to support clinical development of CPL409116 was performed in appropriate species of rodents and non-rodents. Prior to initiation the toxicology assessment a panel of ADMET studies has been performed to evaluate the compound stability and metabolic profile. Based on the results of metabolic profiling Beagle dog was chosen as the non-rodent species, while Wistar Han rat was identified as the most relevant rodent species for the toxicology program. Animal studies were conducted using the administration route that adequately addressed safety concerns in humans. All of the preclinical toxicology studies presented here were conducted in accordance with current ICH regulatory requirements [ICH M3(R2), ICH S3A, ICH S7A, ICH S7B, ICH S2(R1), ICH S5(R2)] as well as in compliance with “Organization for Economic Co-operation and Development” (OECD) principles. Stand-alone pharmacokinetics, dose escalation studies and dose range confirmation studies (7- or 14-day long) were conducted as non-GLP, while repeat dose toxicity studies, genotoxicity, preliminary toxicity of reproduction (segment II) were conducted in compliance with the principles of Good Laboratory Practice (GLP). Furthermore, safety pharmacology studies were performed under GLP regulations as requested by ICH S7A and ICH S7B, and were incorporated into repeat dose studies with the exception of a studies investigating the effect of CPL409116 on hERG K+ currents (conducted as stand-alone in vitro study) and effect on cardiovascular system in telemetrized dogs (conducted as stand-alone in vivo study). Blood samples for exposure and toxicokinetics were taken in all the repeat dose studies and preliminary embryo-fetal development studies. Pharmacokinetic parameters were measured in single dose (intravenous or oral) PK studies using rats and dogs and as part of the repeat dose toxicology studies using rats and dogs (oral). Generally, CPL409116 was absorbed following an oral administration with varied speed with Tmax

between 2 – 8 hours, generally increasing with the dose. The oral bioavailability was 15-50 % for rat females, 16-44 % for rat males and 10.43- 11.73 % for dogs (males and females, respectively).

Single-dose toxicity studies

In all of the in vivo toxicity studies, the CPL409116 compound was administered to the animals (rats, dogs and rabbits) once daily, orally by gavage (rats and rabbits) or capsule (dogs). Single dose escalation toxicity studies of CPL409116 in rats showed no clinical signs nor adverse findings with a dose level up to 450 mg/kg/day (MTD), while studies in dogs indicated toxic potential of CPL409116 (decreased appetite and activity, slight to moderate tremors and vomitus, decreased platelets and reticulocyte counts) with MTD determined as 200 mg/kg/day.

Repeat-dose toxicity studies

CPL409116 administration to rats for 7 days caused increases in liver weights and decrease in spleen and thymus weight at all dose levels. Macroscopic changes included mottled discoloration in different lymph nodes at all dose levels accompanied with sinus erythrocytosis. Microscopic changes in thymus included mainly decreased lymphoid cellularity. NOAEL was determined to be 450 mg/kg/day and doses of 5, 30 and 100 mg/kg/day were selected for GLP Repeated Dose. 14-day repeat dose toxicity study performed in dogs resulted in one unscheduled death in male from middle group (60 mg/kg/day). Animal was euthanized on Day 14 due to a poor and deteriorating condition. Clinical signs observed in the other animals included eyes partly closed and protruding nictitating membrane (at doses ≥ 30 mg/kg/day), decrease in muscle tone, suspected dehydration, hunched posture, decrease in activity and generalized weakness, (at doses ≥ 60 mg/kg/day), abnormal gait and lying on side for 1 male, abnormal respiratory rate for 1 female, tachycardia and shortening of the RR, PR and QT interval at the 6-hour post-dose intervals (at a dose of 120 mg/kg/day). Decrease in red blood cells parameters and significant increase in bilirubin was noted in both genders at 120 mg/kg/day. Thymus weight was decreased up to 62 and 69 % in males and females, respectively with accompanied decreased cellularity (lymphoid) in these animals. NOAEL was determined to be 30 mg/kg/day. In a long-term repeat dose toxicity studies, CPL409116 was administered to the rats and dogs for 91 consecutive days followed by a 28-day recovery period in order to assess the persistence, delayed onset or reversibility of any changes. In rat study, repeated administration of CPL409116 caused a slight decrease in mean body weight and body weight gain at doses ≥ 30 mg/kg/day. Following the 28-day recovery period, the body weight continued to be slightly decreased, whereas body weight gain was increased (for males and comparable to the control animals for females), indicating reversibility of the effect. Decreased counts of all white blood cells was observed at doses ≥ 30 mg/kg/day and decrease in erythrocytes, hemoglobin and hematocrit was observed at 100 mg/kg/day.

At the end of the recovery period, these values were comparable to concurrent controls. No CPL409116-related effects on urinalysis parameters were observed in the male, but in the 17/20 female at 100 mg/kg/day, protein (≥ 3.0 g/L) was noted in the urine (and was still present in 3/5 females at the end of the recovery period). Thymus weight was decreased at doses ≥ 30 mg/kg/day in both sexes up to 78 %, spleen weight was decreased at all doses in females up to 46% and at doses ≥ 30 mg/kg/day in males up to 38 %. At 100 mg/kg/day increase in liver and kidney weight up to 16% was noted in females. At the end of the recovery period, increase in in thymus mean weights in both sexes up to 80%, liver mean weights in males up to 43% and kidneys mean weights in females up to 15% was noted. Spleen mean weights in both sexes were decreased up to 14%, but these values were increased compared to values at the end of main study which suggests ongoing resolution of CPL409116- related splenic findings. Macroscopic changes included discoloration of the lymph nodes at doses ≥ 5 mg/kg/day in females and ≥ 30 mg/kg/day in males. Cysts in the liver were observed: 1/15 females at 30 mg/kg/day and 8/15 females at 100 mg/kg/day and 1/15 males at 100 mg/kg/day. At the end of the recovery period, increased incidence (100% of the animals) of liver cysts was detected in females. Microscopic findings were mostly observed in the hematolymphoid system including the thymus, spleen and lymph nodes (decreased lymphoid cellularity). At 100 mg/kg/day, minimal to mild bile duct hyperplasia in females often accompanied by minimal dilatation of the ducts was observed. NOAEL was determined to be 30 mg/kg/day for females and 100 mg/kg/day for males. In 91 day dog study, repeated administration of CPL409116 caused slight decrease of food consumption in both sexes at all dose levels, without effect on body weight. Decrease of spleen weight was observed at all dose levels up to 50 and 30 % for males and females, respectively. At the end of the recovery period splenic weight changes noted at the terminal euthanasia were no longer observed. NOAEL was determined to be 25 mg/kg/day.

Safety pharmacology

Safety pharmacology study showed no effect of CPL409116 on the cardiovascular system parameters (assessed by radiotelemetry in conscious dogs), nor respiratory functions (assessed by plethysmography in rats), nor central nervous system (investigated as Functional Observational Battery in rats) when compared to the control animals. The genotoxic potential of CPL409116 was assessed in vitro in a bacterial mutation test (Ames test) and a mammalian chromosome aberration assay, both in the presence and absence of a metabolic activation system (S9), as well as in vivo in the rat bone marrow micronucleus test and comet assay. Whereas Ames test did not indicate potential mutagenic activity of CPL409116, significant increase in the incidence of aberrant metaphases were observed in the 4-hour treatment regime, in the presence of S9 mix, at CPL409116 concentrations of 16.0 and 32.0 µg/mL and in the 21-hour treatment regime at a test item concentration of 16.0 µg/mL in chromosome aberration assay.

None of these assays indicated genotoxic potential of CPL409116. Nevertheless, two in vivo tests did not show any genotoxic properties of the tested compound. Reproductive and developmental preliminary toxicity studies (segment II) were conducted in rats and rabbits. In dose escalation studies in female New Zealand White rabbits, the MTD of CPL409116 was 450 mg/kg/day. A repeated dose studies for 7 consecutive days produced evidence of slight to moderate salivation and moderate to severe decrease in food consumption (up to 92%) without changes in body weight. During embryo- fetal development studies in pregnant New Zealand White rabbits following symptoms were observed: vaginal discharge at doses ≥ 100 mg/kg/day, decreased food consumption at doses ≥ 100 mg/kg/day. At 300 mg/kg/day pericardial pale fluid accumulation and thoracic dark fluid accumulation, watery content of the cecum, colon and rectum, dark discoloration/linear foci of the jejunum and a dark linear focus in the stomach in of three different animals was noted. At 100 mg/kg/day: increased post implantation loss associated with an increased number of late resorptions that resulted in a significantly increased total number of resorptions and a slightly decreased number of live fetuses compared to the controls. At 300 mg/kg/day: 1 Female aborted, 1 female had total resorption of its litter (early resorption at each of the 13 implantation sites), and another female also did not have a live litter. The 3 remaining females had viable litters, however, each had between 3 and 6 resorptions, indicative of increased embryo-fetal mortality related to CPL409116. The fetal weights at 100 mg/kg/day were lower than control values. 2 fetuses from separate litters at 30 mg/kg/day and a total of 5 fetuses from 4 litters at 100 mg/kg/day were malformed (subclavian artery, small/depressed right eye bulge, hyperflexion of the right forepaw, herniated diaphragm, absent aortic arch, large and misshapen heart, absent ventricular septum, hyperextension of both hind limbs, hyperflexion of both hind paws, omphalocele, 1 rib absent, 1 branched rib, 1 missing and 2 fused thoracic arches and 2 fused thoracic centra, dilated aortic arch and ventricular septal defect. 1 female from 100 mg/kg/day was euthanized on Day 17 pc due to BW loss between Days 7 and 16 pc and absence of FC between Days 8 and 17 pc, 1 female treated with 300 mg/kg/day on 22 pc was euthanized as it had aborted, 2 females treated with 300 mg/kg/day on GD 19 and 21 were euthanized due to poor condition and 3 surviving females were euthanized. NOAEL for maternal toxicity was considered to be 30 mg/kg/day and the NOAEL for embryofetal development was considered to be 30 mg/kg/day. During embryo-fetal development studies in pregnant Wistar Han rats following symptoms were observed: vaginal discharge, decreased food consumption (up to 37%), decreased body weight (up to 27%) (at all doses). At 30 mg/kg/day increased number of resorptions and the number of early resorptions, decreased number of fetuses at 30 mg/kg/day and decreased gravid uterine weights. At 100 and 300 mg/kg/day, 100 % post implantation loss occurred. No malformations at 30 mg/kg/day were observed for any of the fetuses; the live fetuses at 30 mg/kg/day were all males. Dose levels below 30 mg/kg/day should be considered in subsequent embryo-fetal development studies.

***In vitro* effects of CPL409116 on the hERG channel current (I_{Kr})**

In vitro cardiovascular hERG assay in stably transfected HEK-293 cells showed effect of CPL409116 on hERG current. The IC50 for the inhibitory effect of CPL409116 on hERG potassium current was 1.4 µM (Hill coefficient = 1.1), whereas the positive control article (terfenadine) inhibited hERG potassium current by 88.7 ± 2.3% at 60 nM.

2.3. Summary of Findings from Previous Clinical Studies

[redacted]

2.4. Conclusions from PART IA, PART $IA_{additional}$ and PART B of the clinical trial

[redacted]

[redacted]

2.6. Risk-benefit Assessment

Celon Pharma's product PG24, with CPL409116 as an active ingredient is designed predominantly in therapy of immune-related diseases (rheumatoid arthritis, psoriasis). Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent joint inflammation leading to loss of joint function as well as cartilage and bone damage. Chronic, progressive course of the disease results in disability, reduced quality of life, as well as higher comorbidity and mortality rates (Calabresi 2018s). RA is a disease that affects 0.5 – 1% of adults in developed countries with a higher frequency in women than in men. The aim of RA treatment is to achieve remission or reduction of disease activity by preventing inflammation, progression of joint damage and disability (Smolen 2017). It is well documented that JAK kinases play a pivotal role in cytokine receptor signaling to phosphorylate and activate signal transducer and activator of transcription (STAT) proteins. Several of these JAK-controlled cytokine receptor pathways are immediately involved in the initiation and progression of RA disease pathogenesis. Cytokines promote autoimmunity, maintain chronic inflammatory synovitis and drive the destruction of joint tissue (McInnes 2007). Cytokines are small protein messengers that mediate communications between cells (McInnes 2005). They regulate a variety of bodily processes, including haematopoiesis and are particularly important in the regulation in immunity and inflammation. Cytokines bind to cell surface receptors to initiate a cascade of signaling events that transmit information intracellularly and coordinate the cellular response (Mavers 2009). In RA, B cells, T cells, macrophages and other leucocytes infiltrate the synovium in response to pro inflammatory cytokines and chemokines, leading to inflammation and tissue destruction. Cytokine signaling via JAK pathways leads to further induction of inflammatory gene expression, which continues the loop of inflammatory signaling. Inhibiting cytokine signaling by inhibiting the JAK pathways may, therefore, interrupt the cycle of leukocyte recruitment, activation and pro inflammatory cytokine expression at sites of inflammation (McInnes 2005). The international recommendations for RA treatment acknowledge to achieve clinical remission as a primary treatment goal. The treatment options include nonsteroidal anti-inflammatory drugs (NSAID), glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; such as methotrexate (MTX)), biologic DMARDs (bDMARDs; including tumor necrosis factor (TNF) inhibitors, as well as non-TNF drugs), biosimilar DMARDs and targeted synthetic DMARDs (Smolen 2017). According to the latest guidelines, MTX monotherapy is recommended as a first-line treatment. In patients who fail this treatment due to an inadequate response to or intolerance of MTX, another synthetic DMARD, or a combination of a synthetic DMARD with a bDMARD or targeted synthetic DMARD should be considered depending on the patients conditions. However, RA patients often require therapy for decades and data show that after 2 years only about half of patients remain on their first TNF inhibitor (Harrold 2015).

Treatment options for these patients is to switch to an alternative anti-TNF agent or to switch to a biological agent with different mode of action. Despite these treatment options, some of patients show inadequate responses. Moreover many patients are reluctant to self-inject or undergo iv infusion required for administration of biologics. Additionally, biologic agents require special handling for storage, transportation and administration. Thus, additional treatment options are needed. JAK inhibition with an orally available small molecule represents an alternative approach to biologic therapies.

CPL409116 is a novel kinase inhibitor with enhanced selectivity toward Janus family kinases (JAKs). A structure of CPL409116 has a few functional groups responsible for the activity and selectivity against JAK kinases. Celon Pharma conducted a set of in vitro experiments in order to examine CPL409116 relative potency and selectivity for inhibition of recombinant human JAK and ROCK kinases. CPL409116 selectivity and potency was also tested in vitro experiments on cell lines and primary cells. CPL409116 efficacy in vivo was demonstrated in mouse Collagen Induced Arthritis model and rat model of Pulmonary Hypertension. Based on the preclinical studies the compound has been qualified as a good clinical candidate for the treatment of rheumatoid arthritis.

To determine the appropriate dose for Celon Pharma's PG24 with CPL409116 for phase II clinical trials in patients, a safety and pharmacokinetic study in healthy volunteers was performed. The study was consisted of two parts where the IMP was administered in single and multiple doses. Safety and pharmacokinetic profiles were already determined and according to obtained results it was concluded that CPL409116 is well tolerated and has a promising potential to become a new therapeutic option in patients with rheumatoid arthritis. Moreover, CPL409116 effect on Rho- associated kinases may play a significant role in potential reduction of cardiovascular risk or pulmonary fibrotic changes in patients with RA. Further Celon Pharma's studies are planned in this field.

2.7. COVID-19 risk considerations

Subjects enrolled in the present clinical trial may be determined as at risk of COVID-19 groups because of two immunosuppressive agents administration. The impact of COVID-19 on these patient groups was carefully considered by the Sponsor.

Taking into account the changing epidemiological situation in Poland, Celon Pharma S.A., is going to make every effort to minimalize a health risk for the present trial participants.

The Sponsor is intended to adhere to requirements described in the following document: “Guidance on the management of clinical trial during the COVID-19 pandemic.” Version 3, 28/04/2020 and in its updated versions. Celon Pharma S.A. in cooperation with selected parties and the health center engaged in the described clinical trial is going to undertake following activities in order to limit the negative impact of the epidemiological situation in Poland on the rights and safety of participants and the proceedings of the clinical trial:

- Participants before inclusion to the study are to be tested by using the RT-PCR (real- time reverse transcription polymerase chain reaction) test in order to confirm a lack of infection caused by SARS-CoV-2. The PCR test for SARS-CoV-2 will be performed at Screening (within 72h before baseline). Subjects with a positive result of the test will be excluded from the study.
- Participants are to be asked for filling the questionnaire regarding the previous contact with individuals infected with SARS-CoV-2. The contact of a trial participant with other participants is to be limited to minimalize the risk of infection with coronavirus.
- The health staff engaged in the study is to be acted according to internal procedures to minimalize the risk of infection caused by SARS-CoV-2 spreading.
- 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 quarantine is recommended. 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 trough two weeks after the end of the study if needed. 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 PCR test result.
- Not vaccinated participants who live with a person infected with SARS-CoV-2 will be excluded from the study due to obligatory quarantine.
- It is necessary to fill out 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.
- The present clinical trial consists of 5 ambulatory visits in the main part of the study (12 weeks) to gather appropriate clinical data. The remaining visits will be conducted in the form of phone call visits to limit participants’ contact with the clinical staff and other patients (remote data verification).

- Sponsor in consultation with investigators, fulfilling duties with due caution, is intended to postpone or extend the recruitment process of appropriate number of participants declared in the submitted protocol, if necessary. Sponsor declares that any other action is being taken to protect participants and health staff involved in the study according to "Guidance on the management of clinical trial during the COVID-19 pandemic." Version 3, 28/04/2020, if needed.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary objective

Efficacy:

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

3.2. 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.

[redacted]

4. STUDY DESIGN

4.1. Overview

This is to be 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.

Timepoints for CPL409116/ placebo administration are to be determined according to results obtained in the Phase I clinical trial with CPL409116 (PART A and PART B of the study).

The study is to be consisted 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 administer 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).

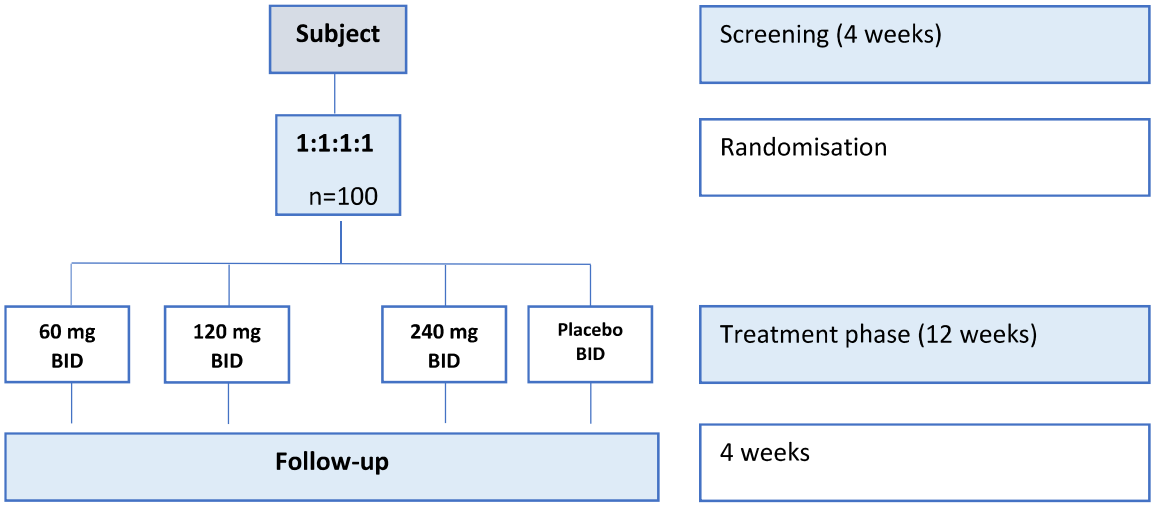


Fig. 3. Overview of the study design.

In the **Screening Period**, patients are to undergo screening assessments from Day -28 to Day 0. Rolling admission is to be employed in this study. Patients that fulfil all the inclusion criteria and none of the exclusion criteria are to 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). Clinical centres must fulfil the following steps of the screening period:

- Informed Consent: written informed consent must be obtained prior to performance of any protocol-specific procedures;
- Review of inclusion/ exclusion criteria: all the inclusion criteria and none of the exclusion criteria must be fulfilled;
- Overview of the subject's demographics, RA history and prior RA medication history (start dates and stop dates with reason for discontinuation, dosage, indication);
- Review of Participant's Medical History, including comorbidities, concomitant (non-RA) medications and previous vaccination (influenza, pneumococcus, herpes zoster, SARS-CoV-2);

- Information about history of alcohol and drug abuse;
- Height and weight measurement;
- Vital signs measurement: sitting blood pressure, pulse, temperature;
- Complete Physical Examination: skin assessment (rash, bruising, cuts, moles, lumps, skin lesions with malignant features), face and eyes abnormalities, neck veins abnormalities, chest and abdomen (observation of any masses, or bulges), legs (swelling), muscles (muscle tone); elbows and joints (swelling, inflammation, deformities); Palpation (abdomen, back or chest wall); Auscultation; The Neurologic Examination;
- 12-lead electrocardiogram (ECG);
- Chest radiograph is required at Screening. A chest X-ray or other appropriate diagnostic chest imaging modality [ie, Computerised Tomography (CT) or Magnetic Resonance Imaging (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;
- Collect blood samples for clinical chemistry, coagulology and hematology;
- Collect blood sample for lipids profile;
- Collect blood sample for ESR testing, RF, ACPA and CRP;
- Collect blood sample for pregnancy test;
- Collect blood sample for FSH testing (WONCBP only);
- Collect urine sample for urinalysis and urine microscopy;
- Confirmation of proper contraception usage;
- Collect blood samples for HIV Serology, HBsAg, HBcAb, HBsAb, HBV DNA, HCVAb and/or HCV RNA;
- Human immunodeficiency virus (HIV) testing is mandatory;
- Collect blood for tuberculosis (QuantiFERON Gold®TM In-Tube) test;
- Collect swab sample for SARS-CoV-2 infection testing (PCR) (72h before Day1) and conduct interview in terms of possible infection with SARS-CoV-2;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Perform assessment of tender and swollen joints RA;
- Evaluation of DAS28-CRP;
- SAE and AE monitoring;
- Randomisation into one of four arms, as follows: 60 mg BID; 120 mg BID; 240 mg BID; placebo).

NOTE: 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 re-scheduled as close to the original visit date as possible.

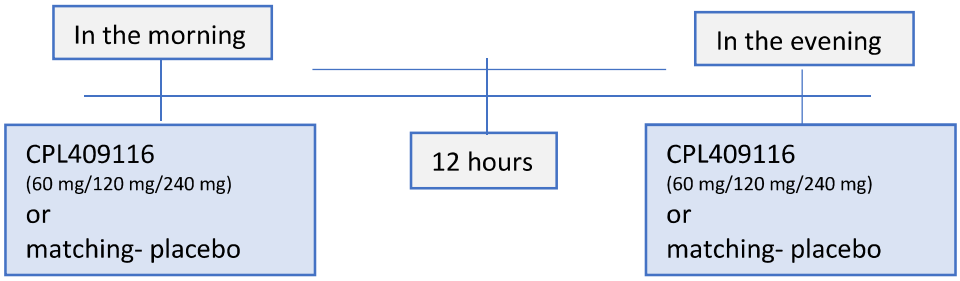


Fig. 4. Dosing sequence scheme during the day. CPL409116 oral administration.

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. Blood samples collection for PK analysis will take place on Day 1/ Baseline; 8; 29; 57 and 85/86.

Moreover, blood samples are to be collected in the treatment period for PD analysis to assess CPL409116 ability to inhibit JAK/ROCK kinases.

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.

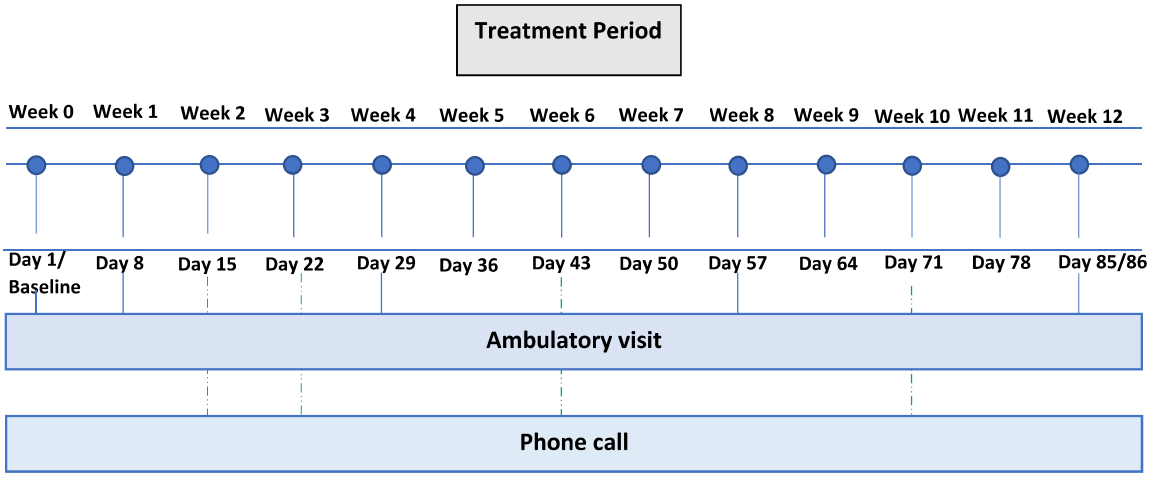


Fig. 5. Scheme of 12-week treatment period. Ambulatory visits and phone call days.

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.

4.2. Scientific Rationale for the Study Design

This *Proof of Concept* study is designed as a multiple-arm trial with three arms of CPL409116 in different dose and one placebo arm. Since the primary goal of the study is to provide an early evidence of anti-inflammatory effect of CPL409116 in rheumatoid arthritis by influence on downstream proteins' phosphorylation as a consequence of JAK/ ROCK inhibition, it is to include placebo arm as the control and investigational drug arm to document clinical benefits. There exist definable conditions that should be fulfilled before placebo-controlled trials is to be proceed. The assessment of these clinical conditions is grounded in the ethical requirements and reflects the current guidance of the OPRR guidelines. For the approval of placebo controls in phase 2 trials some aspects should be considered. First of all rheumatoid arthritis is the well-known disease for which treatment is available however access to some of therapies can be limited (the biologic treatment accessible in therapeutic programs only, injection/ infusion as a route of delivery) and some of them show ineffectiveness in reduction of pathologic changes in joints or do not bring relief in pain. In this placebo-controlled study patients are to administer methotrexate (according to current guidelines MTX is recommended as a first-line RA treatment) which do not bring anticipated effects. During the treatment period patients will be taking painkillers if needed (paracetamol) which should be ceased 24h before an ambulatory visit. Corticosteroids, opioids (tramadol) and NSAIDs are to be continued without change of dosage and route of administration through appropriate period of time before Day 1 of the study in order to avoid any impact of mentioned above drugs on evaluation of IMP effectiveness. The main purpose of this *Proof of Concept* trial is to demonstrate benefits from the JAK/ ROCK inhibitor administration in patients with RA who are treated ineffectively and need new therapeutic options which will be able to improve their quality of life. Nowadays JAK inhibitors are registered, accessible and applied in the treatment of patients with RA, e.g. tofacitinib, hence this mechanism of action is confirmed as an effective solution in autoimmunity. CPL409116 has a dual mechanism of action (JAK inhibition and Rho-associated kinases inhibition) therefore this controlled placebo trial can be the prelude to achieve promising results not only in patients with RA but at the same time in patients with RA complicated by other concomitant diseases.

Doses of CPL409116 which were chosen to phase II of the study had been confirmed as safe and well-tolerated in PART B. Duration of the study equals 12 weeks (3 months) was indicated on the basis of preclinical studies conducted with CPL409116 in rodents (rats) and non- rodents (dogs). It seems to be the sufficient period of time to show effectiveness and tolerance of the investigational product.

4.3. Justification for Dose

[redacted]

4.4. Study Duration

The duration of participation for each patient will be approximately up to 20 weeks. The estimated study duration includes:

- The Screening Period: up to 28 days
- Treatment period: Day 1 to 85/86 days
- Follow-up period: patients are to come to the study centre two times after the last dose of IMP: at Week 14 and Week 16 (Day 99 and Day 113 respectively). On Day 92 and Day 106 the call from the study unit will be made. End of the Study will take place on Day 113, Week 16.

For the entire study, end of the study is defined as the last visit of the last subject for any protocol related activity (last subject, last visit- LSLV).

4.5. Study Completion

A subject is to be considered to have completed the double-blind treatment phase if he/she has completed all the assessments and procedures on Day 113. A subject who, for any reason, discontinues the study before Day 113 will not be considered to have completed the study.

4.6. Early Termination

If a subject withdraws prematurely after dosing, all data normally collected at discharge from the clinical center should be collected at the time of premature discontinuation or at the scheduled discharge. 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.

5. 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).

5.1. Number of Subjects

A total of 100 patients will be enrolled in the Study.

5.2. Inclusion Criteria:

Patients eligible for inclusion in this study have to 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).

5.3. Exclusion Criteria

Patients eligible for inclusion in this study must <u>not</u> fulfill 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 10^9/L (<1500/mm^3);
    c) Absolute lymphocyte count of <0.75 x 10^9/L (<750/mm^3);
    d) Absolute white blood cell (WBC) count of < 3.0 x 10^9 /L (<3000/mm^3);
    e) Hemoglobin <9.0 g/dL (90 g/L);
    f) Thrombocytopenia, as defined by a platelet count <100 x 10^9/L (< 100 000/mm^3) 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. All DMARDs (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.

5.4. Restrictions

Dietary and Fluid Restrictions

Caffeine

Xanthine containing products (e.g., caffeine in coffee, tea, chocolate, energy drinks) will not be allowed from 10 hours before outpatient visit and admission to the clinical centre, and for the time of outpatient visit.

Alcohol

Consumption of alcohol and alcohol-containing foods, medications or beverages must be avoided from 48 hours before admitted to the clinical centre, during whole Treatment Phase until discharge from the clinical centre after completed Treatment Phase. Subjects during the Follow-Up period, are to be required not to consume beverages containing alcohol up to first follow-up visit. Later it is recommended to not consume more than 3 units (males) or 2 units (females) per day (1 unit is equal to approximately ½ pint [284 mL] of beer, one small glass [125 mL] of wine, or one measure [25 mL] of spirits).

Meals during stay at the clinical centre

During in-house stay (Day 85) at the clinical centre only meals and fluid served at clinical centre will be allowed.

Fasting

Dosing on ambulatory visits in the morning will be preceded by an overnight fast of at least (6) hours. Water intake will be allowed up to 1 hour before dosing and from 1 hour after dosing (excluding amount of water allowed for IMP administration). Patients should be fasted 2 hours after IMP administration in the morning and in the evening. In the evening IMP should be administered on fasting condition at least 2 hours after a previous meal.

MTX can be administered together with the Investigational Product however patient should continue the scheme of MTX administration from before the study.

Lifestyle Considerations

Drugs of abuse

Subjects must refrain from use of recreational drugs for the duration of the study.

Nicotine

Cigarette smokers will be allowed to smoke however it is necessary to refrain from smoking 90 minutes before an ambulatory visit.

Strenuous activity

Subjects should refrain from carrying out heavy physical training (e.g., long distance running, weight-lifting, or any physical activity to which the subject is not accustomed) from 48 hours prior to admission to the clinical centre, until the final Follow-up Visit. Subjects should neither start any new physical training nor increase the intensity of their usual training during study participation. Subjects may participate in light recreational activities during study, including rehabilitation allowed by the Investigator.

5.5. Prior and Concomitant Treatments

Any medicinal product prescribed or over-the-counter (OTC), taken by a subject other than the IMP, is considered concomitant medication.

The following concomitant medications may be continued during the study as background RA treatments. The dosage of the basic therapy is not to change for the entire trial from the screening through the end of the study and should be stable within indicated period of time before the randomization process and within dosing with the investigational product.

1. **Methotrexate (MTX)** (required background RA treatment). Subjects will continue on their pre-study dose of MTX (supplemented with folic/folinic acid). Subjects must have been taking oral or parenteral methotrexate for at least 3 months (prior to screening) at an adequate dose to determine that the subject had an inadequate response to MTX. Inadequacy is to be defined by the Investigator's and subject's opinions that the subject did not experience eligible benefits from methotrexate plus the presence of sufficient residual disease activity to meet the inclusion criteria. The MTX dose and route of administration must have been stable for at least 8 weeks before first dose of study drug, and the dose and the route of administration must remain stable during the whole study period. Allowed methotrexate doses are 15 to 25 mg, inclusive, weekly, unless there is documented (epicrisis, the source documentation) intolerance or toxicity from these doses, in which case a dose ≥10 mg, inclusive, may be used.
2. Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including selective Cyclooxygenase-2 inhibitors ("COX-2 inhibitors"), administered according to local guidelines at stable doses 4 weeks before Day1/ baseline.

3. **Opioids** (Tramadol) at a stable dose beginning at least 4 weeks prior to first study dose. Opioids other than tramadol are not allowed during the study and should be ceased at least 4 weeks before Day 1/Baseline.
4. **Paracetamol** at doses 1500 mg (500 mg three times a day) or according to other treatment plans fixed individually. In case of exacerbation of the disease ad hoc administration of paracetamol is permitted. Subjects should refrain from paracetamol 24h before an ambulatory visit.
5. Low dose oral **corticosteroids** at a stable dose ≤10 mg per day beginning at least 4 weeks prior to first IMP dose up to the end of the study. Intravenous, intramuscular and intraarticular administration of corticosteroids is forbidden 6 weeks before Day1/ baseline up to the end of the study. Topical and inhalation corticosteroids are allowed before and during the present clinical trial.

5.6. Prohibited medications:

1. Current therapy with any disease-modifying antirheumatic drug (DMARD) other than MTX. All DMARDs (except for MTX) must be ceased before Day 1/ baseline, as follows:
   - **1 month before**: etanercept, sulfasalazyna, chlorochina/hydroksychlorochina;
   - **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.

2. Previous use of (at any time)
   - Cyclophosphamide
   - Tacrolimus
3. Previous use of JAK inhibitors;
4. 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.

NOTE: Subjects cannot take part collaterally in different clinical trials and administer other IMPs at the same time.

5.7. Rescue medications

Any exacerbation of the disease that requires the implementation of additional rescue therapy requires consultation with the study Sponsor. Each situation will be considered individually.

5.8. Contraception Rules

In order to prevent from pregnancy during the presence clinical trial a woman must be either:

c. Not of childbearing potential:

- postmenopausal (>45 years of age with amenorrhea for at least 12 months, without using exogenous hormonal contraception and with FSH ≥ 40 IU/L),
- 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;

d. 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.

e. 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.

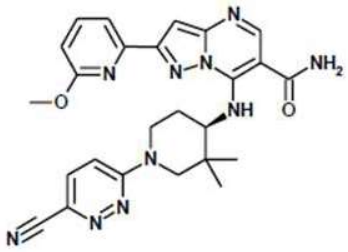
6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1. Physicochemical properties of CPL409116

Active substance: CPL409116

Chemical name: (R)-7-((3,3-Dimethylpiperidin-4-yl)amino)-2-(6-methoxypyridin-2-yl)pyrazolo[1,5-a]pyrimidine-6-carboxamide

Chemical structure:



Molecular formula: $C_{25}H_{26}N_{10}O_2$

Molecular weight 498.55 g/mol

6.2. Identity of the Investigational Medicinal Products

PG24 is to contain CPL409116 (Table 2). It is to be administered in immediate release tablets. Tablet is to be suitable for oral administration. PG24 is to be in tablets containing 60 mg of API (PG242).

Placebo product PG24P also is to be prepared in tablets to correspond to the investigational product (60 mg CPL409116 (PG24P2). Tablet is to be suitable for oral administration.

Table 2. The composition of PG24 and placebo PG24P2.

6.3. Supply, Packaging, Labeling and Storage

CPL409116 compound in formulation (PG24) is to be in tablets containing 60 mg (PG242) of active substance. For the study phase II the PG242 and PG24P2 tablets are to be prepared in the same way in the immediate release formulation. The placebo appearance will be exactly the same as the drug, so that neither the subject nor the Investigators not know what is to be administered.

Tablets are to be packed on three levels. The first is a single aluminum blister in which one tablet is to be closed, consider as a primary package. The aluminum blisters are to provide the tablets with effective protection against moisture and light, what is required for the IMP to retain its properties. Tablets in blisters are to be packed in an outer package- envelopes and cardboard boxes.

Label templates are to be provided in a separate document.

Test item product should be stored at temperature below 25°C.

6.4. Subject Identification and Randomization

Screening Numbers

At Screening, patients will be assigned a unique subject identification number (or subject identifier). Enrolled patients who drop out of the clinical study before randomization will retain their subject identification number.

Randomization Codes

At the end of the Screening, patients will be assigned a randomisation code generated by a randomisation system in the electronic case report form. The randomisation code will consist of four letters. The random coding system is described in a separate document.

Once a randomization code has been allocated to one subject, it may not be assigned to another subject.

6.5. Administration of Investigational Medicinal Products

Starting from Day 1, the IMP will be administered after a minimum 6 hours overnight fast with approximately 250 mL water in the morning. After IMP administration in the morning and in the evening subjects should stay fasted for 2 hours. Patients should be 2 hours fasted before IMP administration in the evening. Subjects must remain in an upright position for at least 1 hour after dosing. MTX can be dosed together with IMP however it is recommended to apply MTX according to a previously fixed treatment plan.

6.6. Dosing

All tablets are to be administered orally. CPL409116 tablets should be taken under fasted conditions (after a minimum 6 hours overnight fast in the morning minimally, 2 hours after the last food consumption in the evening and 2 hours prior to the next meal consumption in the evening), but preferably should be taken consistently in the same manner and at the same time each day. Exceptionally on study visit days patients will be instructed to refrain from dosing at home, and will take the study medication at the clinic. Subjects should swallow the tablets with water to a total volume of approximately 250 mL. It is important that subjects swallow the investigational product whole, and that they not manipulate or chew the investigational product prior to swallowing. Sites will instruct subjects on the proper way to remove tablets from blister packs and how subjects will administer the IMP at home. Subjects will be instructed to self-administer their study medication according to administration instructions provided to the subject. Subjects will be instructed not to remove tablets from the blister packaging until the time of dosing. Patients will be given a subject diary and provided with instructions on the completion of the diary. The diary won't be filled during Patient's visit at Site. The data during ambulatory visits will be recorded in source documentation.

In this phase of the proof of concept clinical trial patients are to take tablets containing 60 mg of IMP (Table 3).

Table 3. The number of tablets for each potential dose of CPL 409116 for the study.

PG24 DOSE	NUMBER OF TABLETS (60 mg)
60 mg	1
120 mg	2
240 mg	4

Patients are to be randomized to one of four study arms with assigned appropriate dose of CPL409116: 60 mg (study arm 1); 120mg (study arm 2) or 240 mg (study arm 3) administered twice a day and with assigned placebo (study arm 4). Every patient included in the study and randomized is to take the same number of

tablets (4 tablets) in the morning and in the evening to blind substances which are to be taken by participants. This number of tablets (4 tablets per administration) is to be corresponding to the highest possible dose of CPL409116 equals 240 mg per administration (4 tablets). The table below shows the number of tablets which are to be taken by participants in particular arms of the study.

Table 4. The number of tablets administered by patients depending on the study arm.

	Study arm	**CPL116 (60 mg) 60 mg per administration**	**CPL116 (60 mg) 120 mg per administration**	**CPL116 (60 mg) 240 mg per administration**	**PLACEBO per administration**	**Total**
Number of tablets	1	1	-	-	3	4
	2	-	2	-	2	4
	3	-	-	4	-	4
	4	-	-	-	4	4

In the clinical unit blisters with appropriate tablets are to be opened by pharmacist or delegated person and prepared for administration in order to eliminate risk of mistake. Patients are to take appropriate number of tablets with active substance or placebo.

6.7. Compliance and IMP Accountability

Dosing will be performed by trained and qualified personnel designated by the Investigator during the ambulatory visits in the morning. The date and time of IMP dosing will be documented on each dosing day during the outpatient visits. During home dosing periods (including evening dosage), time of IMP and methotrexate dosing should be documented in the patient's Diary. Comments will be recorded if there are any deviations from the planned dosing procedures. A single dose is to be consider as a compliant when all 4 tablets are administered, and administration is without any emesis occurring within 2 hours after IMP administration. A patient is to be considered as a complier with dosing regimen when at least 80 % of the doses are compliant (at least 136 doses). Compliance from days of home dosing will be verified by a designated person taking into account data from the Patient's diary and empty blisters patient brings on the next visit and during phone call visits. On Day 85 subjects will be hospitalized up to Day 86 in the morning due to donation of blood samples for PK analysis in 13 timepoints. Subjects can spend Day 85 night to Day 86 outside of the clinic but it is necessary to return on Day 86 in the morning in order to donate the last sample of blood 24h after morning CPL409116 administration on Day 85.The Sponsor shall supply an adequate quantity of the investigational medicinal product (IMP) and the placebo, both for administration and as a backup, along with the respective certificates of analysis (CoA). The amount of each product should be sufficient to account for any loss resulting from its potential damage or subject's withdrawal.

The unblinded pharmacist or delegated person is obliged to store the products in a safe place, with limited access to third parties. The products are to be securely stored under pre-specified conditions, in accordance with applicable regulatory requirements. The products will remain under the supervision of the pharmacist or delegated person and released solely for the administration purposes and IMP dispensing for home dosing, according to the study protocol. On outpatient visits during the treatment phase, patient is to return used blisters and product that was not administered on proper day, and the accountability of the IMP dispensed previously for home dosing will be checked and documented by a designated person. The study designated pharmacist or delegated person is to be responsible for the investigational product in the clinical center during the entire study period. At the end of the study, the number of unused IMP will be determined, and the product will be returned to the Sponsor. Adequate records documenting receipt, use or other disposition of the investigational product will be kept by the designated person. The unblinded study monitor will verify these documents throughout the course of the study.

6.8. Blinding and Breaking the Blind

The clinical study will be performed in a double-blind manner, so the identity of investigational drug and placebo will not be known to investigators, research staff and subjects. At the clinical centers, there is to be an unblinded pharmacist and another unblinded person responsible for the IMP management in accordance with proper pharmaceutical manual. Unblinded staff members are not to be involved in any patient evaluation and examination.

The study blind may be broken only in a medical emergency (where knowledge of the study drug administered would affect the treatment of the emergency). The decision to break the blind will be made on a case-by-case basis, at the discretion of the Investigator, and if possible, in collaboration with the Sponsor and/or Medical Monitor or responsible designee. If the blind is broken, the CRO and Sponsor must be informed as soon as possible. The date, time and reason for unblinding will be documented in the CRF and in the source data. The applicable standard operating procedure (SOP) will be followed for blind breaking procedures.

After database lock, the overall randomization code will be broken only for reporting purposes.

Suspected unexpected serious adverse reactions (SUSARs), that are subject to expedited reporting, should be unblinded by the Sponsor before submission to the regulatory authority and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Information about SUSAR will also be sent to all Investigators (after the patient has been unblinded).

6.9. Treatment of Overdose

In the event of overdose (defined as any dose above that specified in the protocol), the Investigator should contact the CRO and the Sponsor immediately and closely monitor the patient for AEs/SAEs. Supportive symptomatic treatment can be provided for overdose-related AEs. Information regarding the quantity of the excess dose, as well as the duration of the overdosing, should be documented.

Patients should be instructed NOT to take a substitute dose if vomiting occurs after self-dosing at home. Missed doses should be skipped and NOT taken as a double dose at the next dosing timepoint. Missed dose should be recorded.

Symptomatic support measures should be used in the case of excessive pharmacological effects or overdose.

The Investigator should follow-up and document the course and the outcome of each overdose even if the subject was withdrawn from the clinical study or if the clinical study has finished and if the patient agrees. Any SAE that occurs due to overdose must be recorded on the Serious Adverse Event Report Form and must be reported by Investigator to the Sponsor within 24 hours of becoming aware of the event.

7. DISCONTINUATION

7.1. Study Stopping Rules

The stopping rules described in this section of the clinical study protocol (CSP) are applicable to stopping the study. IMP, CPL409116, dosing may be halted temporarily to investigate before the entire study is terminated.

Measures to ensure data integrity and safety of research subjects will be detailed in the Safety Management Plan (SMP) and the Data Management Plan (DMP).

If the Investigator, the Medical Monitor, responsible designee, or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding.

Should the study be terminated, and/or the study center closed for whatever reason, all documentation pertaining to the study and study drug must be returned to the Sponsor. Any actions of the CRO required for assessing or maintaining subject safety will continue as required, despite termination of the study by the Sponsor.

7.2. Safety Criteria

After the first dose of IMP, a subject may discontinue from the study for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other reasons, as determined by the Investigator. If a subject discontinues treatment, their participation in the trial will be discontinued. Discontinued subjects should be encouraged to complete all early termination and Follow-up assessments with early termination assessments conducted as soon as possible after the subject is withdrawn.

An individual subject will be withdrawn from the study if:

- the subject withdraws his/her consent, which he is allowed to do at any time and without the need to justify his/her decision;
- the subject requires treatment with any medication known or suspected to interfere with the study medication;
- the subject is no longer able to participate for other medical reasons (e.g. surgery, adverse event);
- the subject – in spite of the earlier evaluation upon recruitment – is suspected or found not to comply with eligibility criteria;
- there is evidence or sound suspicion that the subject fails to comply with the protocol directives (compliance with the treatment schedule, non-adherence to dietary rules or other study restrictions that may have an influence on study results, non-attendance at study assessments);
- any other condition occurs which in the opinion of the Investigator no longer justifies or permits a safe participation of the subject.

Each patient has the right to withdraw from the study at any time without prejudice. The Investigator may discontinue any patient's participation when he/she feels it is necessary, for any reason including adverse events or Clinical Study Protocol violation. The patient should always be informed about the reason for his discontinuation. Reasons for the withdrawal of an individual patient from the study will be recorded by the Investigator in the Case Report Form and in the Clinical Study Report. In the case of withdrawal caused by an adverse drug reaction, the patient will be under observation until symptoms of the reaction have subsided.

In the case of emesis, an individual patient is to be withdrawn from the study if:

- the subject suffers from moderate or severe emesis within 4 hours in two consecutive IMP administrations. If emesis occurs within 4 hours post-dose and is mild or moderate or emesis occurs

after 4 hours post-dose, discontinuation of the subject depends on the Investigator's judgment and decision.

7.3. Subject Withdrawal and Replacement

In addition to the stopping rules described in Section above a subject will be withdrawn by the Investigator or designee from the study and not be allowed to continue with the study if any of the following criteria are fulfilled:

- If discovered that the subject has entered the study in violation of the inclusion/exclusion criteria stated in the protocol;
- Investigator or the Sponsor stops the study, for any reason (e.g., suspension or discontinuation of study drug development).

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any subject withdraws from the study prematurely. All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical centre should be collected at the time of premature discontinuation or at the scheduled discharge.

Subject participation may be terminated prior to completing the study and the reason recorded as follows:

1. Adverse event;
2. Protocol violation;
3. Loss to Follow-up;
4. Subject withdrew consent at own request;
5. Other.

A genuine effort must be made to determine the reason(s) why a subject fails to return for the necessary visits or is discontinued from the study. At least 3 attempts of telephone contacts must be documented by the site. In case of failure, the patient is considered lost to follow up.

The subject who will be screen failed for not meeting the inclusion or exclusion criteria or will withdraw the consent during the Screening procedures or before the first IMP administration will be replaced by the next qualifying alternate.

The subject who will be withdrawn for any reason or withdraws from the study after any IMP administration or before completing the study, may be replaced by another qualifying alternate but only in case if total number of subjects in a given study arm who would complete the study would be insufficient and there are no safety concerns.

The subject replacement is defined as recruiting additional patients, but it should be remembered that all randomized patients will be analyzed according to the population set definitions described in this Protocol.

The replacing subject is to follow the same treatment and protocol procedures as the withdrawn one. The replacing alternate subject is to receive the study products under the same conditions as the withdrawn subjects, and they are to undergo the entire protocol procedure.

8. STUDY ASSESSMENTS AND PROCEDURES

For timing of assessments, refer to the Schedule of Assessments Table 1.

Eligibility Screening

For patient eligibility screening assessments and procedures, please refer to the Schedule of Assessment Table 1.

Medical History, Demographic and Other Baseline Information:

The medical history comprises:

- General medical history;
- Medication history;
- Reproductive history.

The following demographic information will be recorded:

- Age;
- Race/ethnicity;
- Height, without shoes (cm);
- Body weight, without shoes (kg);
- Body mass index (BMI) (kg/m^2).

Other Baseline characteristics will be recorded as follows:

- History of drug abuse;
- History of alcohol abuse;
- Smoking habits;
- Coffee, tea, and energy drink consumption habits;
- Special diet (vegetarian);
- History of blood or plasma donation.

8.1. Safety Variables

Adverse Events

Adverse event reporting will begin for each subject from the date the informed consent form (ICF) is signed and will continue until the final Follow-up Visit.

Definition of Adverse Event

Any untoward medical occurrence in a subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Other untoward events occurring in the framework of the study will be recorded as AEs, e.g. those occurring during treatment-free periods (including Screening or post-treatment Follow-up periods), in association with study-related procedures and assessments, or under placebo. For study drugs, lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way, e.g., greater in severity.

Concomitant illnesses, which existed prior to entry into the Study, will not be considered AEs unless they worsen during the Treatment Period. Pre-existing conditions will be recorded as part of the subject's medical history.

Definition of Serious Adverse Event

A serious adverse event (SAE) is defined as any adverse event, occurring at any dose and regardless of causality that:

- Results in death;

- Is life-threatening; this means that the subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation in existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in un unexpected manner during the trial (e.g. surgery performed earlier than planned);
- Results in persistent or significant disability/incapacity. Disability is defined as substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly/birth defect;
- Is another important medical event (see below).

Important medical events that do not result in death, are not life-threatening or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in definition of SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in in-patient hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered a SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

Recording of Adverse Events

Adverse events should be collected and recorded for each subject from the date the ICF is signed until the end of their participation in the study, i.e. the subject has discontinued or completed the study.

Adverse events may be reported spontaneously by the subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity and action taken of the AE will be documented together with the Investigator's assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure.

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Assessment of Adverse Events

Each AE will be assessed by the Investigator about the categories discussed in the following sections.

Intensity

The Investigator will assess all AEs for severity in accordance with the following standard ratings:

1. Mild: Ordinarily transient symptoms, does not influence the performance of the subject's daily activities. Treatment is not ordinarily indicated;
2. Moderate: Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on the performance of the subject's daily activities. Treatment may be necessary;
3. Severe: Symptoms cause considerable discomfort. Substantial influence on the subject's daily activities. May be unable to continue in the study and treatment may be necessary.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in the severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade, and the date (and time, if known) of the change.

Causality

The Investigator will assess the causality/relationship between the study drug and the AE. One of the categories described in Table 5 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 5. Assessment of Relationship of Adverse Events to Investigational Product.

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge*) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge† procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

Dechallenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite the withdrawal of the drug, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

†Rechallenge is when a drug suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

Reporting of Serious Adverse Events

The Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to study drug. All SAEs will be recorded from the signing of the ICF until the final Follow-up Visit. Serious AEs occurring after the final Follow-up Visit and coming to the attention of the Investigator must be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

The Investigator is responsible for providing notification to the Sponsor of any SAE, whether deemed IMP-related or not, that a subject experiences during their participation in the study within 24 hours of becoming aware of the event.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS
Notify and send the SAE Report Form and any supporting documentation via email within 24 hours of becoming aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number;
- Patient number;
- Sex;
- Date of birth;
- Name of Investigator and full clinical centre address;
- Details of SAE;
- Criterion for classification as 'serious';
- Study drug name, or code if unblinded, and treatment start date;
- Date of SAE onset;
- Causality assessment (if sufficient information is available to make this classification).

The Sponsor will request clarification of omitted or discrepant information from the initial notification. The Investigator or an authorized delegate is responsible for sending (via email)the requested information to the Sponsor within 24 hours of the Sponsor's request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g. hospital reports, consultant reports, autopsy reports), with the subject's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and sent via e-mail to the Sponsor within 24 hours of receipt of the information. If a new SAE report form is sent , then the Investigator must sign and date the form. The Sponsor may also request additional information on the SAE, which the Investigator or an authorized delegate must send to the Sponsor within 24 hours of the request.

Reporting of Suspected Unexpected Serious Adverse Reaction

Information on SUSARs will be collected and reported to the regulatory authority and the IEC in accordance with European Commission Guidance 2011/C 172/01 or as per national regulatory requirements in the participating country. Details of reporting on country level will be described in the SMP.

Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed or until the subject is lost to Follow-up.

Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the Study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Each pregnancy must be reported by the Investigator to the Sponsor within 2 days after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the Study or if the Study has finished and if the patient agrees.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor on the Pregnancy Report Form within 2 days after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Report Form (e.g., unintended pregnancy after hormonal contraceptive failure, maternal serious complications, therapeutic abortion, spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs using the study SAE report form.

8.2. Clinical laboratory assessments, medical procedures

Samples for clinical laboratory assessments will be collected at the time points detailed in the Schedule of Assessments (Table 1). During administration days, samples will be collected pre-dose (≤ 1h before IMP administration). Samples will be collected in appropriate tubes and handled according to standard procedures of the applicable laboratory. Clinical laboratory variables will be determined as outlined in Table 6.

Table 6. Clinical laboratory assessment.

Hematology	
White blood cell (WBC) count	Neutrophils (percentage and absolute count)
Red blood cell (RBC) count	Lymphocytes (percentage and absolute count)
Hemoglobin (Hb)	Monocytes (percentage and absolute count)
Hematocrit (HCT)	Eosinophils (percentage and absolute count)
Mean corpuscular volume (MCV)	Basophils (percentage and absolute count)
Mean corpuscular hemoglobin (MCH)	Platelet count
Mean corpuscular hemoglobin concentration (MCHC)	Red cell distribution (RDW)
Coagulation	
Prothrombin time (PT)	International Normalized Ratio (INR)
Activated partial thromboplastin time (APTT)	
Clinical Chemistry	
Alanine aminotransferase (ALT)	Gamma glutamyl transferase (GGT)
Albumin	Glucose
Alkaline phosphatase (ALP)	Lactate dehydrogenase (LDH)
Aspartate aminotransferase (AST)	Phosphorus
Blood urea nitrogen (BUN)	Potassium
Calcium	Sodium
Chloride	Total bilirubin
Creatinine	Total protein
Creatine kinase (CK)	Uric acid
Follicle stimulating hormone (FSH) (Screening Visit only, for applicable postmenopausal female subjects)	
Other	
Anti CCP Antibodies (ACPA)	
Rheumatoid Factor (RF)	
Erythrocyte Sedimentation Rate (ESR)	
C Reactive Protein	
Lipid profile	
HDL	
LDL	
Total cholesterol	
Triglycerides	
Urinalysis	
Bilirubin	Blood
Glucose	pH and specific gravity
Ketones	Protein
Leukocytes	Urobilinogen
Nitrite	

Microscopic	
Viral Serology	
Hepatitis B surface antigen (HBsAg); HBcAb; HBsAb Hepatitis C virus antibody (anti-HCV); HCV RNA; HBV DNA	Human immunodeficiency virus (HIV) (Types 1 and 2) antibodies
Tuberculosis	
QuantiFERON	
COVID-19	
PCR test (SARS-CoV-2)	
Urine Drug Screening Test	
Amphetamines Barbiturates Benzodiazepines Cannabinoids	Cocaine Opiates Phencyclidine
Pregnancy Testing	
Serum/urine human beta chorionic gonadotrophin (women of childbearing potential only)	

Any value outside the normal range will be flagged for the attention of the Investigator or qualified designee at the site. The Investigator or designee will indicate whether the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during the Screening Period is indicated as clinically significant, the subject will not be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the Follow-up Visits, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized, at the discretion of the Investigator.

QuantiFERON Test

A QuantiFERON Gold®™ is a simple blood test that aids in the detection of Mycobacterium tuberculosis, the bacteria which causes tuberculosis (TB). This test will be used to test for active / latent tuberculosis (TB). QFT is an interferon-gamma (IFN-γ) release assay, commonly known as an IGRA, and is a modern alternative to the tuberculin skin test (TST, PPD or Mantoux).

A description of the QuantiFERON Gold test follows: “This Enzyme-linked Immunosorbent Assay (ELISA) test detects the release of Interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides simulating two proteins present in M. tuberculosis: Early Secretory Antigenic Target--6 (ESAT-6) and Culture Filtrate Protein-10 (CFP-10). ESAT-6 and CFP-10 are secreted by all M. tuberculosis and pathogenic M. bovis strains. Because these proteins are absent from all Bacille Calmette-Guérin (BCG) vaccine strains and from commonly encountered NonTuberculous Mycobacteria (NTM) except M. kansasii, M. szulgai, and M. marinum, QFT-G is expected to be more specific for M. tuberculosis than tests that use tuberculin Purified Protein Derivative (PPD) as the antigen.”

Subjects with a documented positive 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. The type and results of the IGRA TB test must be known and enclosed to the source documentation.

Chest X-Ray

Chest radiograph (posterior-anterior and lateral views are recommended) is required at Screening. A chest X-ray or other appropriate diagnostic chest imaging modality [ie, Computerised Tomography (CT) or Magnetic Resonance Imaging (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.

Alcohol test

An estimation of blood alcohol content from a breath sample is to be performed to determine if subject is not under influence of alcohol.

Vital Signs

Vital signs will be assessed at the time points detailed in the Schedule of Assessments (Table 1).

Vital signs assessment that indicates the status of the body’s vital function is to be performed. These measurements are taken to help assess the general physical health of a person and include: body temperature (BT), blood pressure (BP) and heart rate (pulse, HR).

BT is to be measured predose, measurements at the other time-points are up to investigator discretion.

Blood pressure will be measured in the subject's dominant arm and recorded to the nearest mmHg. The same arm will be used throughout the study. All blood pressure in this study will be measured with the subject in the sitting or lying position after resting for at least 5 minutes. The same blood pressure cuff, which has been properly calibrated, should be used to measure blood pressure each time. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained first.

Standard 12-lead Electrocardiograms

Standard safety 12-lead ECGs will be performed at the time points detailed in the Schedule of Assessments (Table 1).

Recording of the electrical activity of the heart over a period of time using electrodes placed on the skin, meaning electrocardiography (ECG) is to be performed. This is to be a 12-lead ECG, with electrodes placed on the subject limbs and on the surface of the chest. Then the overall magnitude of the heart's electrical potential is measured from 12 different angles and is recorded over a period of time. ECG is to be recorded after at least 5 minutes resting period. The ECG results will be stored in the study database and used for the planned analysis. If blood sampling or vital signs measurement are to be scheduled at conflicting with ECG recording time point, the procedures are to be performed in this order: ECG, vital signs, blood sampling.

Physical Examinations

Physical examinations will be performed at the time points detailed in the Schedule of Assessments (Table 1).

An assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic systems).

Phone call contact

Phone call day prior to admission to the clinical center or outpatient visit is to be made in order to remind Subject about the visit, conditions (e.g. fasting conditions, urine sample), bringing IMP and used blisters, completed Patient's Diary and other necessary things and/or documentation. Interview of the Subject's condition, to monitor symptoms of potential presence of viral or bacterial infection is to be made. This is to include, among others, body temperature and symptoms such as cough, dyspnea, sore throat and others.

All phone call visits need to include: collecting data about adverse events, concomitant medications, interview of the Subject's overall condition and any other questions, on the Investigator's discretion.

8.3. Pharmacokinetics [redacted] Variables

PK Blood Sample Collection

Blood for the analysis of CPL409116 will be collected at the time points detailed in the Schedule of Assessments (Table 1) and as detailed in Table 7.

Table 7. Timepoints for blood samples collection for PK analysis.

	Day1/ baseline	**Day 8**	**Day 29**	**Day 57**	**Day 85/ Day 86**
	Pre-dose 0.0 ≤ 30 min before CPL409116 administration in the morning	Pre-dose 0.0 ≤ 5min before CPL409116 administration in the morning	Pre-dose 0.0 ≤5 min before CPL409116 administration in the morning	Pre-dose 0.0 ≤5 min before CPL409116 administration in the morning	Pre-dose 0.0 ≤5 min before CPL409116 administration in the morning
After CPL409116 administration	0.5 h	0.5 h	2.5h	0.5 h	0.5 h
	1.0h	1.0h		1.0h	1.0h
	1.5h	1.5h		1.5h	1.5h
	2.0h	2.0h		2.0h	2.0h
	2.5h	2.5h		2.5h	2.5h
	3.0h	3.0h		3.0h	3.0h
	4.0h	4.0h		4.0h	4.0h
	6.0h	6.0h		6.0h	6.0h
					8.0h
					10h
					12h
					24h

Blood samples for PK analysis are to be collected on the following Days: 1/Baseline; 8; 57 (timepoints: pre-dose and 0.5; 1.0; 1.5; 2.0; 2.5; 3.0; 4.0; 6.0h (+/- 5 min) after CPL409116 administration in the morning) and on Day 29 in the following timepoints: pre-dose (0.0) and 2.5h (+/-5 min) 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; 24h (+/-5 min) after CPL409116 administration in the morning.

Blood samples are to be collected, centrifuged, processed and stored for analysis in accordance with bioanalytical laboratory specified procedure, which is to be provided before the start of the study.

Total blood loss due to exploratory PK analysis is to be ca.**189 mL** per each subject.

[redacted]

8.4. Efficacy

American College of Rheumatology (ACR) Assessments

The specific components of the ACR Assessments (ACR Core Dataset) that are to be used in this study are:

a) Tender/Painful Joint count (TJC) (68);

b) Swollen Joint Count (SJC) (66);

c) Patient's Assessment of Arthritis Pain;

d) Patient's Global Assessment of Arthritis;

e) Physician's Global Assessment of Arthritis;

f) C-Reactive Protein (CRP);

g) Erythrocyte Sedimentation Rate (ESR);

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

Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale: Present/Absent/Not Done/Not Applicable- artificial joints will not be assessed.

The 68 joints to be assessed are: temporomandibular, sternoclavicular, acromioclavicular shoulder, elbow, wrist, metacarpophalangeals, thumb interphalangeal, proximal interphalangeals, distal interphalangeals; hip, knee, ankle, tarsus, metatarsophalangeals, great toe interphalangeal, proximal and distal interphalangeals combined.

Swollen Joint Count (66)

There will be assessed joints for swelling using the following scale: Present/Absent/Not Done/Not Applicable- for artificial or missing joints. Sixty-six (66) joints will be assessed for swelling, the same as those listed above for tenderness/pain, except that the right and left hip joints are not included in the swollen joint count. Artificial joints will not be assessed.

Tender and Swollen Joint Counts (28)

The twenty-eight tender/painful joint count includes the following joints: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, interphalangeal joints of the thumb and knees.

Patient's Assessment of Arthritis Pain (PAAP)

Patients will assess the severity of their arthritis pain using a 100 mm visual analogue scale (VAS) by placing a mark on the scale between 0 (no pain) and 100 (most severe pain), which corresponds to the magnitude of their pain. This assessment must be performed early in the clinic visit and before the subject has extensive contact with site personnel and/or investigator.

Patient's Global Assessment (PtGA) of Arthritis

Patients will answer the following question, "Considering all the ways in which your rheumatoid arthritis affected you, how do you feel about your arthritis today?" The patient's response will be recorded using a 100 mm visual analogue scale (VAS). This assessment must be performed early in the clinic visit and before the subject has extensive contact with site personnel and / or investigator.

Physician's Global Assessment (PhGA) of Arthritis

The investigator will assess how the patient's overall arthritis appears at the time of the visit. This is an evaluation based on the patient's disease signs, functional capacity and physical examination, and should be independent of the Patient's Global Assessment of Arthritis. The investigator's response will be recorded using a 100 mm visual analogue scale (VAS).

Health Assessment Questionnaire – Disability Index (HAQ-DI)

The HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in daily living activities, for instance: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and others. There are 2 or 3 questions for each section. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). For each section the score given to that section is the worst score within the section, i.e. if one question is scored 1 and another 2, then the score for the section is 2. In addition, if an aide or device is used or if help is required from another individual, then the minimum score for that section is 2. If the section score is already 2 or more then no modification is made. This questionnaire must be performed early in the clinic visit and before the subject has extensive contact with site personnel and / or investigator. The form should then be checked by the site staff for completeness.

ACR Responder Analysis

The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant which for this study will be CRP. Similarly, ACR50 and ACR70 are calculated with the respective percent improvement.

Disease Activity Score (DAS) Assessments

The Disease Activity Score (DAS) assessment is a continuous composite measure derived using differential weighting given to each component. DAS28 is a measure based on 28 tender and swollen joint counts. The components of the DAS 28 arthritis assessment include:

- Tender/Painful Joint Count (28);
- Swollen Joint Count (28);
- CRP;
- VAS disease activity (0-100mm).

SF-36 RAND

The SF-36 RAND is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. These domains can also be summarized as physical and mental component scores. This must be performed early in the clinic visit and before the subject has extensive contact with site personnel and / or investigator. The form should be checked for completeness by the site staff.

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

The FACIT – F is a patient completed questionnaire consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (less fatigue). This questionnaire must be performed early in the clinic visit and before the subject has extensive contact with site personnel and/or investigator. The form should then be checked by site staff for completeness.

8.5. Exploratory Analyses

Evaluation of the CPL409116 ability to inhibit STAT, MYPT and MLC phosphorylation by inhibition of JAK and ROCK kinases activity in patients with active RA. In the study tagged antibodies against phosphorylated STAT1, STAT5, MYPT1 and MLC are to be used. The influence of test compound on the phosphorylation status of signaling molecules is to be determined by comparison of fluorescence intensity in blood samples obtained before and after test compound administration and measured by a reliable detection method, for example FACS (fluorescence-activated cell sorting).

Exploratory PD analysis results are to be presented in separate document, other than Clinical Study Report.

8.6. Total Amount of Blood

The maximum volume of blood planned for collection from each subject over the course of the entire study (from the Screening Visit to the final Follow-up Visit, but not including repeat or additional tests ordered by the Investigator) will not exceed **470 ml** and presents no undue risk to the subjects.

9. STUDY SCHEDULE

The study is to include 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 IMP administrations per day in the morning and in the evening (except Day 85 with CPL409116 administration in the morning only, and except Day 86 without CPL409116 administration and with donation of the last sample of blood for PK analysis). Ambulatory visits will take place on Day 1, 8, 29, 57 and 85/86. Phone calls will be made on Day 15, 22, 43 and 71.
- A 4 weeks post-treatment follow-up phase up to Week 16 (Day 113). Patients are to come to the study centre two times after the last dose of IMP. Every week (for 4 weeks after the last IMP administration) there is to be contact with patients: an ambulatory visit or phone call 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).

9.1. Screening

In the Screening Period, patients are to undergo screening assessments from Day -28 to Day 0. Rolling admission is to be employed in this study. Patients that fulfil all the inclusion criteria and none of the exclusion criteria will be considered eligible for the study. Subjects must complete all screening procedures and assessments and have test results available prior to the baseline visit (Visit 2). Subjects who do not have all tests completed within screening period or who temporarily do not meet study entry criteria (random reasons) may be re-screened one time with prior Sponsor approval. Clinical centres must fulfil the following steps of the screening period:

- Informed Consent: written informed consent must be obtained prior to performance of any protocol-specific procedures;
- Review of inclusion/exclusion criteria: all the inclusion criteria and none of the exclusion criteria must be fulfilled;
- Overview of the subject's demographics, RA history and prior RA medication history (start dates and stop dates with reason for discontinuation, dosage, indication);
- Review of Participant's Medical History, including comorbidities, concomitant (non-RA) medications and previous vaccination (influenza, pneumococcus, herpes zoster, SARS-CoV-2);
- Information about history of alcohol and drug abuse;
- Height and weight measurement;
- Vital signs measurement: sitting blood pressure, pulse, temperature;

- Complete Physical Examination: skin assessment (rash, bruising, cuts, moles, lumps, skin lesions with malignant features), face and eyes abnormalities, neck veins abnormalities, chest and abdomen (observation of any masses, or bulges), legs (swelling), muscles (muscle tone); elbows and joints (swelling, inflammation, deformities); Palpation (abdomen, back or chest wall); Auscultation; The Neurologic Examination;
- 12-lead electrocardiogram (ECG);
- Chest radiograph is required at Screening. A chest X-ray or other appropriate diagnostic chest imaging modality [ie, Computerised Tomography (CT) or Magnetic Resonance Imaging (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;
- Collect blood samples for clinical chemistry, coagulology and hematology;
- Collect blood sample for lipids profile;
- Collect blood sample for ESR testing, RF, ACPA, CRP*;

  * CRP must be assessed two times at Screening, the first time up to 72h before Day1/baseline (for evaluation of DAS28-CRP) and the second time within the 72-hour period before Day1/baseline to use a measurement result for DAS28-CRP evaluation on Day1/ baseline.

  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;
- Collect blood sample for pregnancy test;
- Collect blood sample for FSH testing (WONCBP only);
- Collect urine sample for urinalysis and urine microscopy;
- Confirmation of proper contraception usage;
- Collect blood samples for HIV Serology, HBsAg, HBcAb, HBsAb, HBV DNA HCVAb and/or HCV RNA;
- Human immunodeficiency virus (HIV) testing is mandatory;
- Collect blood for tuberculosis (QuantiFERON Gold®TM In-Tube) test;
- Collect swab sample for SARS-CoV-2 infection testing (PCR) (72h before Day 1/ baseline) and conduct interview regarding possible SARS-CoV-2 infection;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Perform assessment of tender and swollen joints RA;
- Evaluation of DAS28-CRP

- SAE and AE monitoring.
- Randomisation into one of four arms, as follows: 60 mg BID; 120 mg BID; 240 mg BID; placebo).

NOTE: 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.

9.2. 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, Day 85- only one dose of CPL409116 in the morning). 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 re-scheduled as close to the original visit date as possible. The desired solution in this case is to schedule the visit within the Window Visit indicated in the schedule assessment: +/-2 Days based on Week 0/Day 1. Visit Window for Patient ambulatory visit **is not applicable for Day 85**, due to the end of Treatment Period and endpoints assessments. In case of other, prolonged deviations consultations with the Sponsor are required.

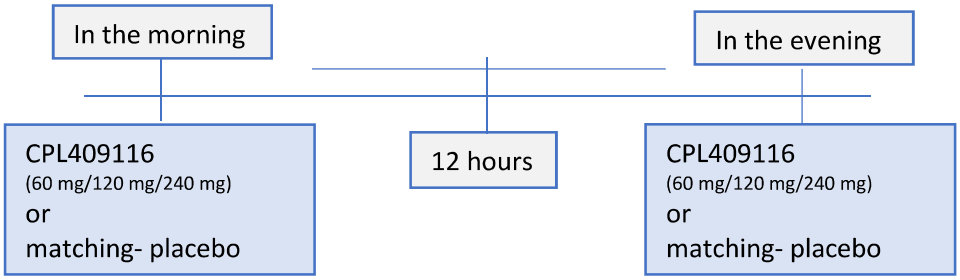


Fig. 6. Dosing sequence scheme during each day. CPL409116 oral administration.

Visit 2 Baseline Day 1/ Week 0

Patients are required to be fasted for at least 6 hours prior to the visit. The following assessments should be done before other study related procedures and before significant contact with the principal investigator and site personnel:

The patient reported outcome assessments:

1. Patient's Assessment of Arthritis Pain;
2. Patient's Global Assessment of Arthritis;
3. Health Assessment Questionnaire - Disability Index (HAQ-DI);
4. SF-36 RAND;
5. FACIT Fatigue Scale.

The Investigator is to review all inclusion/exclusion criteria. If the subject is able to continue, the following activities should be conducted:

Procedures that will be performed pre-dose:

DAS28-CRP/ ACR Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Physician's Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI); SF-36 RAND, FACIT-fatigue scale; Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis (scales filled out by the subject should be verified by the Investigator if it is filled out correctly and all answers were given).

- Questionnaire regarding possible SARS-CoV-2 infection;
- Review current and prior Medication and Treatments (RA and non RA);
- Measure vital signs: sitting blood pressure, pulse, and temperature;
- Perform complete physical examination;
- Perform 12-lead electrocardiogram;
- Collect blood samples for chemistry, haematology and the coagulation profile laboratory assessments;
- Collect blood sample for local ESR assessment;
- Collect blood samples for RF, ACPA and CRP (including testing 72h before visit);
- Collect blood samples for lipid profile assessment;
- Collect urine sample for laboratory urinalysis and urine microscopy;
- Collect urine for pregnancy testing (women of childbearing potential, only);
- Confirm proper contraception is being used;

- Collect urine sample for toxicology tests (alcohol breath test and urine drug test);
- Collect blood samples to the PK analysis (≤30 min before IMP administration);
- [redacted]

Administration of IMP/ placebo and next:

- Collect blood samples to the PK analysis 0.5; 1.0; 1,5; 2.0; 2.5; 3.0; 4.0 and 6.0h (+/- 5 min) after CPL409116 administration;
- [redacted]
- Dispense investigational product/ placebo;
- Dispense a diary part to subject and instruct subject on proper use of the diary;
- Dispense of Patient's card
- Adverse events monitoring.

Visit 3, Day 8/Week 1

Procedures that are to be performed on Visit 3, include:

- Questionnaire regarding possible SARS-CoV-2 infection;
- Review Treatments (RA and non RA) and concomitant Medication taking into account resctrictions of the study;
- Measure vital signs: sitting blood pressure, pulse, and temperature;
- Perform targeted physical examination;
- 12-lead electrocardiogram;
- Collect blood samples for chemistry, haematology and the coagulation profile laboratory assessments;
- Collect blood sample for CRP, RF, ESR and lipid profile assessment;
- Collect urine sample for laboratory urinalysis and urine microscopy;
- Collect urine for urine pregnancy testing (women of childbearing potential);
- Confirm proper contraception is being used;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Collect blood samples for the PK analysis (≤ 5 min before IMP administration);

Administration of CPL409116 or placebo;

a. Collect blood samples to the PK analysis 0.5; 1.0; 1,5; 2.0; 2.5; 3.0; 4.0 and 6.0 (+/-5 min) after CPL409116 administration;

b. Review of the diary for compliance with daily diary completion;

c. Provide subject retraining as required concerning dosing instructions and compliance;

d. Dispense a diary part to subject and instruct subject on proper use of the diary;

e. Dispense investigational product/ placebo;

f. Collect used blisters;

g. Adverse events monitoring.

Phone call Visit, Day 15/Week 2

Phone call is to be made in order to:

1. remind a subject about the ambulatory visit taking below listed aspects into account:
    - conditions (e.g. fasting condition)
    - IMP and used blisters
    - filling out the diary.
2. Interview of the Subject's condition:
    - symptoms of potential presence of viral or bacterial infection (e.g. body temperature, symptoms such as cough, dyspnea, sore throat and others, questionnaire regarding possible SARS-CoV-2 infection).

All phone call visits need to include:

- collecting data about adverse events, concomitant medications, interview of the Subject's overall condition and any other questions, on the Investigator's discretion.

Phone call visit, Day 22/Week 3

Phone call is to be made in order to:

- remind a subject about the ambulatory visit taking below listed aspects into account:
    - conditions (e.g. fasting condition)
    - IMP and used blisters
    - filling out the diary.
- - Interview of the Subject's condition:
    - symptoms of potential presence of viral or bacterial infection (e.g. body temperature, symptoms such as cough, dyspnea, sore throat and others, Questionnaire regarding possible SARS-CoV-2 infection);

All phone call visits need to include:

- collecting data about adverse events, concomitant medications, interview of the Subject's overall condition and any other questions, on the Investigator's discretion.

Visit 4, Day 29/Week 4

Procedures that will be performed on Visit 4, Day 29/Week 4 include:

Patients are required to fast for at least 6 hours prior to the visit. The following assessments should be done before other study related procedures and before significant contact with the principal investigator and site personnel:

The patient reported outcome assessments:

- Patient's Assessment of Arthritis Pain;
- Patient's Global Assessment of Arthritis;
- Health Assessment Questionnaire - Disability Index (HAQ-DI);

Procedures that will be performed pre-dose:

- Questionnaire regarding possible SARS-CoV-2 infection;
- DAS28-CRP/ ACR Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI) (scales filled out by the subject should be verified by the Investigator if it is filled out correctly and all answers were given);
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Measure vital signs: sitting blood pressure, pulse, and temperature;
- Collect blood samples for chemistry, coagulation and hematology laboratory assessments;
- Collect blood sample for ACPA, CRP, RF, ESR and lipid profile assessment ;
- Collect urine sample for laboratory urinalysis and urine microscopy;
- Collect urine for urine pregnancy testing (women of childbearing potential, only);
- Confirm proper contraception is being used;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;

- Collect blood samples for the CPL409116 PK analysis (pre-dose, ≤5 min before IMP administration);

Administration of CPL409116 or placebo;

- Collect blood samples to the PK analysis 2.5h (+/- 5 min) after CPL409116 administration;

[redacted]

- Review of the diary for compliance with daily diary completion (and provide subject retraining as required);
- Dispense subject a part of the diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study treatment;
- Dispense investigational products;
- Collect used blisters;
- Serious and non-serious adverse events monitoring.

Phone call visit, Day 43/Week 6

Phone call is to be made in order to:

- remind a subject about the ambulatory visit taking below listed aspects into account:
  - conditions (e.g. fasting condition)
  - IMP and used blisters
  - filling out the diary.

- Interview of the Subject's condition:

- symptoms of potential presence of viral or bacterial infection (e.g. body temperature, symptoms such as cough, dyspnea, sore throat and others, Questionnaire regarding possible SARS-CoV-2 infection);

All phone call visits need to include:

- collecting data about adverse events, concomitant medications, interview of the Subject's overall condition and any other questions, on the Investigator's discretion.

Visit 6, Day 57/Week 8

Patients are required to be fasted for at least 6 hours prior to the visit. The following assessments should be done before other study related procedures and before significant contact with the principal investigator and site personnel:

The patient reported outcome assessments:

- Patient's Assessment of Arthritis Pain;
- Patient's Global Assessment of Arthritis;
- Health Assessment Questionnaire - Disability Index (HAQ-DI).

Procedures that will be performed pre-dose:

- DAS28-CRP/ ACR Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI);
- Questionnaire regarding possible SARS-CoV-2 infection;
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature;
- Perform targeted physical examination;
- Collect blood samples for chemistry, coagulation and hematology laboratory assessments;
- Collect blood sample for ACPA, CRP, RF, ESR and lipid profile assessment ;
- Collect urine sample for laboratory urinalysis and urine microscopy;
- Collect urine for urine pregnancy testing (women of childbearing potential, only);
- Confirm proper contraception is being used;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Collect blood samples to the PK analysis (≤5 min before IMP administration)

Administration of CPL409116 or placebo;

- Collect blood samples to the PK analysis 0.5; 1.0; 1,5; 2.0; 2.5; 3.0; 4.0 and 6.0h (+/- 5 min) after CPL409116 administration;

[redacted]

- Review of the diary for compliance with daily diary completion (and provide subject retraining as required);

- Dispense a part of a subject diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study;
- Dispense investigational product;
- Collect used blisters;
- Serious and non-serious adverse events monitoring.

Phone call visit 7, Day 71/Week 10

Phone call is to be made in order to:

- remind a subject about the ambulatory visit taking below listed aspects into account:
    - conditions (e.g. fasting condition)
    - IMP and used blisters
    - filling out the diary.
- - Interview of the Subject's condition:
    - symptoms of potential presence of viral or bacterial infection (e.g. body temperature, symptoms such as cough, dyspnea, sore throat and others, Questionnaire regarding possible SARS-CoV-2 infection);

All phone call visits need to include:

- collecting data about adverse events, concomitant medications, interview of the Subject's overall condition and any other questions, on the Investigator's discretion.

Visit 8, Day 85/Week 12

Patients are required to be fasted for at least 6 hours prior to the visit. The following assessments should be done before other study related procedures and before significant contact with the principal investigator and site personnel:

The patient reported outcome assessments:

- Patient's Assessment of Arthritis Pain;
- Patient's Global Assessment of Arthritis;
- Health Assessment Questionnaire - Disability Index (HAQ-DI);
- SF-36 RAND
- FACIT-fatigue scale.

Procedures that will be performed pre-dose:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Health Assessment Questionnaire –Disability Index (HAQ-DI); SF-36 RAND, FACIT-fatigue scale;
- Questionnaire regarding possible SARS-CoV-2 infection;
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature;
- Perform targeted physical Examination;
- 12-lead electrocardiogram;
- Collect blood samples for chemistry , coagulation and hematology laboratory assessments;
- Collect blood sample for ACPA, CRP, RF, ESR and lipid profile assessment ;
- Collect urine sample for laboratory urinalysis and urine microscopy;
- Collect urine for urine pregnancy testing (women of childbearing potential, only);
- Confirm proper contraception is being used;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Collect blood samples for the CPL409116 PK analysis (≤ 5 min before IMP administration in the morning);

Administration of CPL409116 or placebo in the morning;

Morning dose is the last dose of IMP taken by subject during this study.

- Collect blood samples to the PK analysis 0.5; 1.0; 1,5; 2.0; 2.5; 3.0; 4.0; 6.0; 8.0,10, 12h and 24h after CPL409116 administration in the morning on Day 85.

[redacted]

- Review of the diary for compliance with daily diary completion (and provide subject retraining as required);
- Collect used blisters;
- Serious and non-serious adverse events monitoring.

NOTE: 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); 0.5; 1.0; 1.5; 2.0; 2.5; 3.0; 4.0; 6.0; 8.0; 10; 12; 24h 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 center on Day 86 in the morning to donate the last blood sample 24h after morning CPL409116 administration on Day 85.

Day 86/ Week 12

- Continuation of one-day hospitalization from Day 85 to Day 86 or return to the study center on Day 86 in the morning to collect the last blood sample for PK analysis. Blood sample is to be collected 24h after CPL409116 administration on Day 85 in the morning;
- Serious and non-serious adverse events monitoring;
- Study center discharge and the end of the treatment period.

9.3. Follow-up Period

Phone call visit, Day 92/Week 13

Phone call is to be made in order to:

- remind a subject about the ambulatory visit taking below listed aspects into account:
    - conditions (e.g. fasting condition)
- - Interview of the Subject's condition:
    - symptoms of potential presence of viral or bacterial infection (e.g. body temperature, symptoms such as cough, dyspnea, sore throat and others Questionnaire regarding possible SARS-CoV-2 infection;

All phone call visits need to include:

- collecting data about adverse events, concomitant medications, interview of the Subject's overall condition and any other questions, on the Investigator's discretion.

Follow-Up/Visit 9, Day 99/Week 14

Procedures that will be performed on Visit 9, Day 99/Week 14 include:

- Questionnaire regarding possible SARS-CoV-2 infection;

- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Measure vital signs: sitting blood pressure, pulse, and temperature
- Perform complete physical examination;
- Collect blood samples for chemistry laboratory assessments; haematology and coagulology;
- Collect blood sample for CRP, RF, ESR and lipid profile assessment;
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Collect urine for urine pregnancy testing (women of childbearing potential, only);
- Confirm proper contraception is being used;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Serious and non-serious adverse events monitoring.

Phone call visit, Day 106/Week 15

Phone call is to be made in order to:

- remind a subject about the ambulatory visit taking below listed aspects into account:
    - conditions (e.g. fasting condition)
- - Interview of the Subject's condition:
    - symptoms of potential presence of viral or bacterial infection (e.g. body temperature, symptoms such as cough, dyspnea, sore throat and others, Questionnaire regarding possible SARS-CoV-2 infection);

All phone call visits need to include:

- collecting data about adverse events, concomitant medications, interview of the Subject's overall condition and any other questions, on the Investigator's discretion.

Follow-Up/Visit 10, Day 113/ Week 16

The following assessments should be done before other study related procedures and before significant contact with the principal investigator and site personnel:

The patient reported outcome assessments:

- Patient's Assessment of Arthritis Pain;
- Patient's Global Assessment of Arthritis;
- Health Assessment Questionnaire - Disability Index (HAQ-DI);

- SF-36 RAND;
- FACIT-fatigue scale.

Procedures that will be performed on Visit 10, Day 113/Week 16 include:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Health Assessment Questionnaire –Disability Index (HAQ-DI); SF-36 RAND; FACIT-fatigue scale;
- Questionnaire regarding possible SARS-CoV-2 infection;
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature;
- Perform complete physical Examination;
- 12-lead electrocardiogram;
- Collect blood samples for chemistry, haematology and coagulology laboratory assessments;
- Collect blood sample for ACPA, CRP, RF, ESR and lipid profile assessment;
- Collect urine sample for laboratory urinalysis and urine microscopy;
- Collect urine for urine pregnancy testing (women of childbearing potential, only);
- Confirm proper contraception is being used;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Serious and non-serious adverse events monitoring;
- Register the subject's status as completed and discharge the subject from the study.

9.4. Early Withdrawal

In case of early withdrawal patients are to be undergone following procedures:

The following assessments should be done before other study related procedures and before significant contact with the principal investigator and site personnel:

The patient reported outcome assessments:

- Patient's Assessment of Arthritis Pain;
- Patient's Global Assessment of Arthritis;
- Health Assessment Questionnaire - Disability Index (HAQ-DI);

- SF-36 RAND;
- FACIT-fatigue scale.

Procedures that will be performed in case of early withdrawal include:

- DAS28-CRP/ ACR Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire –Disability Index (HAQ-DI); SF-36 RAND; FACIT-fatigue scale;
- Questionnaire regarding possible SARS-CoV-2 infection;
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature;
- Perform complete physical Examination;
- 12-lead electrocardiogram;
- Collect blood samples for chemistry , haematology and coagulology laboratory assessments;
- Collect blood sample for local ESR assessment;
- Collect blood samples for RF, ACPA, CRP;
- Collect blood samples for lipid profile assessment;
- Collect urine sample for laboratory urinalysis and urine microscopy;
- Collect urine for urine pregnancy testing (women of childbearing potential, only);
- Confirm proper contraception is being used;
- Collect urine sample for toxicology tests (presence of drugs in urine), alcohol breath test;
- Review of the diary for compliance with daily diary completion;
- Collect used blisters;
- Serious and non-serious adverse events monitoring.

10. STATISTICAL CONSIDERATIONS

Before database lock, a Statistical Analysis Plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the Clinical Study Report (CSR).

10.1. General considerations

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, SD, minimum, median and maximum). Categorical data will be summarized by treatment group using frequency tables (both number and percentage).

10.2. Study Population

Patient Disposition

Patients excluded from the safety and PK analysis sets and data excluded from the PK analysis sets will be listed, including the reason for exclusion. Patient disposition will be summarized and will include the following information: number of patients randomized and dosed, number and percentage of patients completing the study and the number and percentage of patients who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all randomized patients.

Patients' discontinuations will be listed, including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent responses will also be presented.

A randomization listing will be presented and include the following: each subject's/patient's randomization number, the patient's full enrolment number, the treatment to which the subject/patient has been randomized and the location of the clinical center.

Protocol Deviations

All protocol deviations will be listed by subject. Protocol deviations will be handled in accordance with the CRO SOPs.

Analysis Populations

- Full Analysis Set (FAS): All randomized patients.
- Intent to Treat Set (ITT): All randomized patients that received 1 dose of IMP (60 mg, 120 mg or 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 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 or 240 mg CPL409116 or placebo).

- Pharmacokinetic Analysis Set (PS): All patients in the SS with at least 1 evaluable PK parameter and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism and excretion of CPL409116.
- Pharmacokinetic Set for parameter calculation (PSPC): All subjects in the safety set with extensive PK sampling that has at least 1 PK parameter evaluable and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism, and excretion of CPL409116.

The FAS will be the primary analysis set used for all efficacy analyses and the PP will be used for supportive analyses of the primary and selected 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.

10.3. Evaluation of Efficacy

Primary endpoint analysis

Primary endpoint is change from baseline in (DAS)28-C Reactive protein (CRP) score at 12 weeks.

Analysis will include data on all CPL409116 arms and placebo. The primary analysis will be conducted on ITT analysis set with analysis of PP subset being supplementary to the main analysis.

The null hypothesis is that there are no differences in the primary endpoint between either dose group compared to placebo, versus the alternative hypothesis, that at least 1 dose group is significantly different, using a 2-sided 5% significance level. The primary endpoint will be analyzed using a mixed effect repeated measures model (MRMM), with treatment, timepoint and clinical site as fixed effects and baseline score as a 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. The primary analysis will compare each dose group with placebo at Week 12.

Missing values due to a patient dropping from the study for lack of efficacy or adverse event, will be handled by setting the (DAS)28-C Reactive protein (CRP) score to last observation carried forward (LOCF).

Sensitivity analysis of primary endpoint will include MRMM model with pooled CPL409116 arms vs placebo. Details of this and other sensitivity analyses of primary endpoint will be described in the SAP.

Secondary Endpoints Analyses

Change from baseline in DAS28-CRP score at week 4, 8, 12 and 16 will be analyzed on basis of LS-means calculated by MRMM model used in primary endpoint analysis without adjustment for multiplicity.

Proportion of subjects with DAS28-CRP remission on Week 12 (score <2.6) in each study arm will be presented together with confidence intervals and p values calculated using proportion test (adjusted for multiple comparisons). A logistic regression model with baseline DAS28-CRP, treatment and clinical site as independent variables will be also prepared to explain occurrence of remission. Median time to remission will be estimated using Kaplan-Meier method.

ACR20, ACR 50, ACR 70, and ACR 90 responder rates on Weeks 8 and 12 will be presented descriptively. Differences between CPL409116 arms and placebo will be presented together with confidence intervals and p values calculated using proportion test (adjusted for multiple comparisons). Logistic regression models with baseline DAS28-CRP, treatment and clinical site as independent variables will be also prepared to explain achievement of response.

Change from baseline in the Tender/Painful and Swollen Joint Count (Weeks 8 and 12) and change from baseline in PhGA of Arthritis (Weeks 8 and 12) will be analyzed using MRMM models (using respective baseline values, dose and clinical site as fixed effects and subject as random effect. These analyses will be performed without adjustment for multiplicity.

Further details of secondary endpoints' analyses will be provided in the SAP.

10.4. Demographic and Anthropometric Information and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight and BMI) will be listed by subject and summarized by treatment and for all subjects in the safety analysis set. The denominator part for percentages will be the number of subjects in the safety analysis set for each treatment or for all subjects as applicable.

Screening and baseline values for vital signs, physical examination, 12-lead ECG, chest X-ray and rheumatoid arthritis baseline characteristics will be presented descriptively.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA system organ class (SOC), MedDRA PT, start date, and stop date (or ongoing if applicable).

10.5. Prior and Concomitant Medication and Drug Administration

Prior medications are those that started and stopped prior to the first dose of IMP. Concomitant medications are those taken after first dosing (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed by subject and will include the following information: reported name, preferred term, the route of administration, dose, frequency, start date/time, duration and indication.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD) latest version.

Drug administration dates and times will be listed for each subject.

10.6. Exposure

A listing of drug administration will be created and will include the date and time of administration. When appropriate, a summary table of compliance will also be created.

10.7. Safety Analyses

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations.

Adverse events

All AEs will be listed. The number and percent of subjects experiencing an event will be tabulated for each SOC and preferred term. The AEs will also be tabulated according to intensity and causality.

Clinical Laboratory Tests

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listings. Clinical laboratory tests (observed values) will be summarized descriptively in tabular and graphical format. Shift tables will be presented for select laboratory parameters.

Vital signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Individual clinically significant vital signs findings that were considered AEs by the Investigator will be presented in the AE listings.

Observed values, as well as change from baseline data, will be summarized descriptively in tabular and graphical format.

12-lead Electrocardiogram

Standard 12-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values will be summarized descriptively in tabular format. Change from baseline will be summarized descriptively for QTc data. A categorical QTc analysis will also be performed.

Physical examination

Abnormal physical examination findings reported since screening visit will be listed.

10.8. Pharmacokinetics Analyses

The concentration of CPL409116 and its M3 metabolite in plasma will be summarized by dose at each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. Plasma PK parameters for CPL409116 will be summarized by dose for subjects with extensive PK using descriptive statistics. Additional analysis, if deemed appropriate, will be described in the SAP.

The concentration-time data will be summarized descriptively in tabular and graphical formats (linear and log scales). The PK parameter data will be listed and summarized descriptively in tabular format.

10.9. Patient Reported Outcomes

Change from baseline in:

- Patient's Assessment of Arthritis Pain (PAAP) VAS;
- Patient's Global Assessment of Arthritis (PtGA, VAS);
- Health Assessment Questionnaire – Disability Index (HAQ-DI);
- SF-36 RAND questionnaire;
- FACIT-F

will be presented descriptively for each timepoint. Description of additional analyses will be provided in the SAP.

11. ANALYSIS OF OTHER ENDPOINTS

Analysis of other endpoints will be conducted as deemed appropriate. Details of other endpoint analyses will be outlined in the SAP.

11.1. Interim analyses

No formal interim analysis is planned.

11.2. Determination of 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 post-intervention. 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.

12. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

12.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, Celon Pharma S.A. or its representative will ensure the following:

- development and provision of instructional material to the study sites, as appropriate;
- start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures as well as IMP handling and management;
- periodic monitoring visits to the study site by Clinical Research Associates;
- availability for consultation and regular contact with the study site personnel by mail, telephone, and/or fax;
- revision and evaluation of CRF data and use standard computer edits to detect errors in data collection;
- quality review of the database.

Celon Pharma SA or its representative will periodically check a sample of the patient data recorded against source documents at the study site during monitoring visits.

The study may be also audited by Celon Pharma S.A. or a designee, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the Study for each study participant. Frequent communication between the clinical centre and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the Study will be carefully monitored with respect to Good Clinical Practice (GCP) and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure the integrity of the data and will periodically review the progress of the study with the Investigator.

Protocol deviations will be handled in accordance with the CRO's SOPs.

12.2. Data Collection and Access to Source Data/Documents

Celon Pharma SA will use an electronic data capture (EDC) system to completely collect all medical data during this study. EDC system is a software tool designed similarly to an electronic medical record for the documentation of e.g., medical history, demographics, vital signs, and AEs.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. System supported data collection processes and procedures are validated to ensure completeness, accuracy, reliability and consistency. A complete audit trail is maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks (plausibility and completeness) will be used along with the Investigator's review to identify any errors or inconsistencies in the data. Data clarification requests will be provided to the study team by means of electronic or manual queries.

During the study setup, adequate and accurate clinical procedure forms are used to generate medical records, digital ECGs, AE and concomitant medication reporting, raw data collection forms, etc., which are designed as a protocol to record all observations and other pertinent data for each subject receiving study medication. The only regularly used paper-based study document is the ICF, because it requires wet-ink signatures. The ICFs will be archived in paper form at the end of the study.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors and the IEC to have direct access to all electronic records pertaining to the study.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification.

12.3. Archiving Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to the CRO procedures.

The Investigator's Site File will be archived by the clinical centre for 15 years after completion of the Study. The Trial Master File will be archived by the Sponsor for 15 years after completion of the Study.

12.4. Good Clinical Practice

The procedures set out in this CSP are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP. The Study also will be carried out in keeping with national and local legal requirements.

12.5. Informed Consent

Eligible patients may only be included in the study after providing IRB/IEC approved informed consent.

Informed consent must be obtained from the patient before conducting any study-specific procedure.

As part of the informed consent procedure, the Investigator must explain orally and in writing the nature, duration and purpose of the study and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences or AEs that may occur. The patient should be informed that he/she is free to withdraw from the study at any time. Patient s will receive all information that is required by federal regulations and ICH guidelines. The ICF must be signed and dated; one copy will be handed to the patient, and the Investigator will retain a copy as part of the Study records. The Investigator will not undertake any investigation specifically required for the Study until written consent has been obtained. The terms of the consent and when it was obtained must be documented in the patient source documents.

The Sponsor will review the investigator-proposed ICF to ensure it complies with the ICH GCP guideline (including the ethical principles that have their origins in the Declaration of Helsinki) and regulatory requirements and is considered appropriate for this Study.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all patients subsequently enrolled in the Study, as well as those currently enrolled in the Study as applicable.

12.6. Insurance and Compensation for Injury

The Sponsor has covered this Study by means of insurance of the Study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

12.7. Protocol Approval and Amendments

Before the start of the Study, the CSP and other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the Study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff and receive IRB/IEC approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated CSR. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

12.8. Confidentiality Data Protection

The CRO and the Sponsor will take appropriate measures to ensure the processing of personal data and the free movement of such data are handled according to the European Union General Data Protection Regulation 2016/679.

All Study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, not by name. Documents that identify the subject (e.g., the signed ICF) must be maintained in confidence by the Investigator.

12.9. Publication Policy

By signing the CSP, the Investigator agrees with the use of results of the Study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

13. REFERENCE LIST

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SIGNATURE PAGE

Declaration of the Investigator

I have read and understood the protocol version 3.0, dated 20.12.2022, specified below, and agree on the contents.

Protocol Title: 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.

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current risk and benefit evaluation of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice applicable to this clinical study.

I have read all pages of this clinical study protocol, version 3.0, dated 20.12.2022 and confirm that it contains all the information required to conduct this study. I agree to conduct the study as detailed in the protocol and comply with all the terms and conditions set out therein. I confirm that I is to conduct the study in accordance with the provisions of the Declaration of Helsinki. I will also ensure that Investigator(s) and other relevant members of my staff have access to copies of this protocol and the Declaration of Helsinki to enable them to work in accordance with the provisions of the documents and standard operating procedures of designated CRO company. Furthermore, current ICH-GCP, and local regulations is to be followed.

I acknowledge that all data included in the clinical study protocol are confidential. Copying, disclosing and publishing without assent of Sponsor is prohibited.

Investigator's Signatory

Signature	Date

Name	
Title	
Institution	