

Official Title: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTI-CENTER PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RO7123520 AS ADJUNCT TREATMENT IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO TNF- α INHIBITORS

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PROTOCOL

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TEST PRODUCT: RO7123520

SPONSOR: F. Hoffmann-La Roche Ltd

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FINAL PROTOCOL APPROVAL

Approver's Name

[REDACTED]

Title

Company Signatory

Date and Time (UTC)

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PROTOCOL ACCEPTANCE FORM

TITLE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RO7123520 AS ADJUNCT TREATMENT IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO TNF- α INHIBITORS

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I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please keep the signed original form in your study files, and return a copy to your local Study Monitor.

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol BP39261 version 3 has been amended to incorporate the following changes:

Patients receiving intravenous administration with infliximab (or biosimilars) were previously excluded due to the potential risk of developing anti-drug antibodies (ADA). However, as the patients in this study are receiving methotrexate and possibly other non-biological DMARDs in line with the primary objective, this should prevent the formation of ADA (based on multiple studies, as summarized by Jani et al 2014). Inclusion criteria are therefore modified to permit patients receiving infliximab (or biosimilar) to be enrolled.

In Part 2, the patient's dominant hand/ wrist is assessed with magnetic resonance imaging (MRI) to ensure that only patients with active rheumatoid arthritis (RA) will be enrolled. This criterion has been modified so the non-dominant hand can also be assessed, as disease activity might otherwise be missed.

Concomitant treatment with non-biological agents such as sulfasalazine, leflunomide and gold salts were prohibited in the study. However, as it is permitted to treat patients with the non-biological Disease Modifying Anti-Rheumatic Drug (DMARD) methotrexate (MTX), other non-biological agents will be allowed in addition to MTX. No safety concerns are expected due to the non-overlapping mode-of-actions and toxicities between RO7123520 and tumor necrosis factor (TNF) inhibitors, MTX and combination with other non-biologic DMARDs.

The dose range of MTX has been modified to include a lower dose, i.e., 5.0 mg/week (instead of 7.5 mg/week) to allow for country-specific differences in dosing.

The age of the study population has been expanded to include patients older than 80 years of age. This allows patients with elderly-onset RA to be captured. Although this group of patients may have many concomitant medications, there are no concerns about including very elderly patients as differences in pharmacokinetics and drug-drug interactions are not anticipated.

The wording of inclusion criterion 6 has been adjusted to *recommended and stable dose* instead of *approved and stable dose*, as it is not intended to limit the investigators' country-specific approvals.

Sections on overdose and reporting have been updated in line with new requirements from the Sponsor's GCP council, with impact on company protocol templates and electronic case report forms (eCRFs). The protocol templates have been updated with

language to account for special situations (overdose, medication error, drug abuse, and drug misuse).

Other:

- Exclusion criterion for *requiring* major surgery updated to *planned* surgery.
- The joint chosen for synovial fluid aspiration will be at the Investigator's discretion. The time points of synovial fluid aspiration versus synovial biopsy samples have been clarified (inconsistency with the Schedule of Assessment tables).
- *Complete* versus *symptom-directed* physical examination clarified.
- As testing for drugs of abuse are not actively requested at screening, the text on drug panel was removed from the laboratory assessments.
- Adjustments for local laboratory test reporting: only if required for AE/SAE or for erythrocyte sedimentation rate (optional).
- The analysis method enzyme-linked immunosorbent assay (ELISA) for measuring soluble cadherin-11 has been replaced by *immunoassay*.
- The Brief Fatigue Inventory (BFI) from 1997 has been replaced by the BFI of 1999, which was the version used for the ePRO programming.
- The Schedule of Assessment tables have been updated as applicable. Additionally, minor consistency errors have been corrected.

References:

Jani M, Barton A, Warren RB, et al. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology*; 2014; 53:213-222.

PROTOCOL AMENDMENT, VERSION 4: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

3.1.1.2. Part 2: Phase IIa Proof-of-Concept Study

...

In Part 2 only, patients will undergo contrast-enhanced MRI imaging of the ~~dominant hand/wrist~~, *the site to be determined by the Investigator*, to confirm disease activity at baseline and examine joint changes in patients with active RA on MTX and inadequate response to anti-TNF- α therapy.

...

The study will proceed to Part 3 if there are no more than one-third of the patients who received RO7123520 reporting serious study drug-related adverse events of a similar nature (e.g., laboratory abnormalities, vital sign changes, ECG changes, etc.) ~~or~~*and* if there are no other reasons to stop the study (see Section 4.7.2).

3.2.5. Rationale for Biomarker Assessments

Cadherin-11 expression in synovium and synovial fluid might differ from patient to patient which might impact the response to the treatment. The expression of Cad-11 in the synovium ~~will-might~~ be measured by tissue staining while the soluble form of Cad-11 will be measured ~~by ELISA~~ (shed Cad-11) *in* the synovial fluid of patients who consented to the sampling. *Blood soluble Cad-11 concentrations which might vary upon treatment may be measured by immunoassay*~~ELISA~~.

MRI scans will be performed to assess disease severity for patients in Study Part 2. Inflammatory lesions in the joints and the bone erosion will be evaluated, and soft tissue and bone marrow involvement will be assessed. The readings will be done centrally, by a blinded reader.

As active synovitis of the ~~dominant~~ hand/wrist as determined by MRI is an inclusion criterion for active disease in Part 2 (Section 4.2.2), the central reader will also give the confirmation that this criterion is met.

3.3.4. Exploratory Outcome Measures

Change from baseline in Cad-11 synovium level ~~and~~ in synovial fluid *and* blood soluble Cad-11 concentration at Weeks 12 and 24

4.2.2. Inclusion Criteria

2. Adult men and women, *of more than 18 to 80 years of age (inclusive)*.
5. For Part 2 only: Active synovitis and/or osteitis ~~of the dominant hand/wrist~~ as determined by contrast-enhanced MRI.
6. Patients must be taking one of the following anti-TNF- α therapies: certolizumab, golimumab, etanercept, adalimumab, *infliximab* or approved biosimilars of these, given at a *recommended approved* and stable dose for at least 12 weeks before randomization, and have experienced in the opinion of the Investigator an inadequate response to anti-TNF- α therapy with a DAS28 ≥ 3.2 .
Note: prior use of other anti-TNF- α therapies is allowed.
7. Patients must be taking MTX (PO, SC, or IM) for at least 12 weeks before randomization and must be on a stable dose for at least 4 weeks before randomization (5.07.5 to 25 mg/week).
- ...
8. Patients on glucocorticoids (≤ 10 mg/day PO prednisone or equivalent) are permitted if doses are stable within 6 weeks of planned randomization.
Note: Patients should remain on stable doses of glucocorticoids throughout the duration of study unless for *medical reasons* (e.g., safety, or intolerance, *RA flare, etc*-reasons).

4.2.3. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. ~~Currently receiving concomitant treatment with sulfasalazine or leflunomide.~~
2. ~~Note: Enrollment is allowed after an appropriate wash-out period (i.e., 5 half-lives).~~
3. ~~Patients currently on IV infliximab or an approved IV biosimilar of it are excluded.~~
4.
 1. Parenteral glucocorticoids administration (IM, IV) of ≥ 50 mg within 6 weeks or ≤ 50 mg within 4 weeks prior to planned randomization, or scheduled parenteral administrations during the study.
 - ...
 14. Major surgery within 28 days prior to randomization, or ~~requiring planned~~ major surgery (e.g., elective joint replacement surgery) during the trial.

4.5 Concomitant Treatment

Patients must be receiving stable regimens of MTX (i.e., 7.55.0 to 25 mg/week, per oral, subcutaneous, or intra-muscular application) and at least one anti-TNF- α therapy (from

the following certolizumab, golimumab, etanercept, adalimumab, *infliximab* or approved biosimilars of these) in order to be eligible for the study. The *recommended* dose of anti-TNF- α therapy should be stable for at least 12 weeks, and the dose of MTX should be stable for at least 4 weeks before randomization. The doses should not be adjusted during the study except for safety or intolerance reasons.

Local standard-of-care should be followed for concomitant administration of folic acid.

Where possible all other concomitant medications (e.g., glucocorticoids, NSAIDs) should be kept stable during the study and only adjusted where clinically indicated, *e.g., as in RA flare.*

4.5.1. Prohibited Therapy

The following medications are prohibited after randomization:

- Live vaccines, including herpes zoster vaccination. Non-live seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed.
- Any biologic therapy such as anti-IL-1, anti-IL-6, or T-cell or B-cell targeted therapies for any indication.
- Any interferon therapy for any indication.
- Any parenteral corticosteroid administered by IV injection.
- ~~Concomitant RA treatment with sulfasalazine, leflunomide, or gold salts.~~

4.6.1.2. Physical Examination

A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, and neurological systems *and should be done as indicated in Appendix 1.*

Any abnormality identified at baseline should be recorded on the appropriate eCRF.

Height (screening only) and weight will be recorded.

Additionally, or as clinically indicated, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.6.1.6. Laboratory Assessments

...

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for ~~an positive abnormal urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.~~

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the ~~local~~ or central laboratory. *Local laboratory analysis should only be used for study parameters related to AE/SAE. Erythrocyte sedimentation rate (ESR) may be performed locally.*

Samples for the following blood and urine laboratory tests will be collected and sent to the appropriate laboratory for analysis according to the lab manual:

- Hematology: leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
~~erythrocyte sedimentation rate [ESR], HsCRP~~

...

4.6.1.10 Biomarker Assessments

Blood, Urine, Plasma and Serum Samples

Whole Blood, urine, plasma and serum samples will be collected for the following assessments:

- Multi-biomarker disease activity (MBDA) test
- Bone remodeling and cartilage markers (e.g., CTX-I, PINP and osteocalcin)
- Safety biomarkers which will include T cells, B cells, NK cells, granulocyte and monocyte markers.

Plasma/serum samples may also be used for analysis of inflammatory, synovial and angiogenesis markers.

Urine samples will be collected to measure CTX-II.

Synovial Fluid Samples

Synovial fluid aspiration, which will be done at – two timepoints (or three in case of optional extension; see Appendix 1 and Appendix 2), can be performed from the same joint being biopsied but should precede the biopsy. Samples will be processed for routine histology, immunohistochemistry and RNA expression, several protein biomarkers assessments and may be used for measuring RNA expression. The joint used for fluid aspiration is at the Investigator's discretion. If possible, the same joint should be aspirated during the study.

Synovial Biopsy Samples

Synovial biopsy samples will be taken by arthroscopy under local anesthesia at four timepoints at two timepoints (or three in case of optional extension; Appendix 1 and Appendix 2). Samples will be processed for routine histology, immunohistochemistry and potentially to assess RNA expression. The joint used for synovial biopsy is at the Investigator's discretion. If possible, the same joint should be assessed during the study.

Immunohistochemistry of Synovial Tissue

The immunohistochemical analyses may include the following markers: ~~Gad-11~~ CD106, ~~CD68~~ CD55, ~~CD68~~, IL-8.

4.6.1.11 Disease-Specific Assessments

MRI

For Part 2 only: Fat-suppressed, T1-weighted 3D gradient-echo and short tau inversion recovery (STIR) images of the dominant hands/wrists will be obtained with and without gadolinium contrast using 1.5T MRI and a hand frame to ensure reproducible positioning.

5.3.5.11. Overdoses

~~Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.~~

~~Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.~~

~~All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).~~

5.4 Immediate Reporting Requirements from Investigator to Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies
- *Accidental overdoses or medication errors (see Section 5.4.4. for details on reporting requirements).*

5.4.4. Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- *Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose*
- *Medication error: accidental deviation in the administration of a drug*
In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with RO7123520, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- *Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.*

- *Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.*

For RO7123520, each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4). For RO7123520, adverse events associated with special situations should be recorded as described below for each situation:

- *Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

6.8 Exploratory Analyses

Potentially Prognostic and Disease Severity Biomarkers

The potentially prognostic and disease severity biomarkers (MBDA and CTX-II, Section 3.2.5) will be summarized descriptively at Baseline by treatment/dose arm. In addition, the synovium cadherin-11 ~~measure~~^{data-and}, synovial fluid and blood soluble cadherin-11 data will be summarized descriptively by visit and treatment/dose arm. Those biomarkers will be summarized using the efficacy analysis population.

Appendix 1 and 2, Schedule of Assessment tables

The Schedule of Assessment tables have been revised to reflect the changes in the protocol (in Appendix 1 [Main table for Parts 1, 2 and 3] and Appendix 2 [Main table, Optional Extension for Parts 1, 2 and 3]).

Appendices 8 and 10

The BFI from 1997 has been replaced by the BFI of 1999 (Appendix 8). The text for the morning stiffness assessment (Appendix 10) has been updated with the text used in the ePRO.

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PROTOCOL SYNOPSIS

TITLE	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RO7123520 AS ADJUNCT TREATMENT IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO TNF-α INHIBITORS
PROTOCOL NUMBER:	BP39261
VERSION:	3
EUDRACT NUMBER:	2016-002126-36
IND NUMBER:	112,481
TEST PRODUCT:	RO7123520
PHASE:	II
INDICATION:	Rheumatoid Arthritis
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES

Primary Objectives

The primary objective of this study is:

- To assess the safety, tolerability and efficacy of RO7123520 as adjunctive treatment with methotrexate (MTX), and anti-TNF- α therapy in patients with moderately to severely active rheumatoid arthritis (RA) with an anti-TNF- α inadequate response (Study Parts 1,2,3).

Secondary Objectives

The secondary objectives for this study are as follows:

- To assess the dose-ranging efficacy of RO7123520 (Study Part 3).
- To assess the exposure versus response relationship and immunogenicity of RO7123520 (Study Parts 1,2,3).

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To explore biomarker changes in serum, plasma, urine, synovial fluid and synovial tissue (Study Parts 1,2,3).
- To explore biomarker changes and their relationship with clinical efficacy endpoints (Study Parts 1,2,3).
- To explore joint changes by magnetic resonance imaging (MRI; Study Part 2).

STUDY DESIGN

Description of Study

This is a Phase IIa/b double-blind, placebo-controlled, randomized, parallel group, global multicenter study to evaluate the safety and efficacy of RO7123520 as adjunctive therapy in patients with RA who are inadequately responding to standard-of-care (MTX and anti-TNF- α therapy).

Patients with moderately to severely active RA will be recruited if they experience an inadequate response to disease-modifying anti-rheumatic drug (DMARD) therapy with MTX plus anti-TNF- α therapy for at least 3 months before randomization. This first- and second-line therapy will be continued throughout the study. The MTX and anti-TNF- α dose and product should not be changed during the study, unless for safety or intolerance reasons, until the primary endpoint assessment. All patients will receive concomitant folic acid supplementation as per local standard-of-care. The randomization will be stratified by the patient's duration of prior anti-TNF- α therapy (3-12 months vs > 12 months) for Study Parts 2 and 3.

The study will be conducted in three parts. A final safety visit will occur 8 weeks (German sites: 16 weeks) after the patient's final study dose, regardless of the study part of the last received dose.

Part 1: Safety Cohort

A safety cohort of patients with moderately to severely active RA will be treated with RO7123520 as adjunctive therapy with MTX and anti-TNF- α therapy. Nine patients will be

randomized in a 1:2 ratio and will receive placebo (N=3), or RO7123520 360 mg/dose as adjunct treatment (N=6). In Part 1 dosing will be staggered and no more than two patients will be dosed on any given day. Four doses of RO7123520/placebo will be given as intravenous (IV) infusions on Days 1, 14, 28 and 56. A double-blind design will be used with placebo-administered patients receiving IV infusions of saline only. When all of the nine patients in Part 1 have reached the Day 42 (Week 6) visit, i.e., two weeks after the 3rd dose administration, an Internal Monitoring Committee (IMC) along with an external Scientific Oversight Committee (SOC) will perform a safety review on unblinded data. The SOC and the IMC will advise the clinical trial team of their opinion on the study conduct.

The study will proceed to Part 2 if there are no more than one-third of the patients who received RO7123520 reporting serious study drug-related adverse events of a similar nature (e.g., laboratory abnormalities, vital sign changes, ECG changes, etc.) or if there are no other reasons to stop the study.

All patients in Part 1 will have the option of continuing to the Extension Period of the study.

Part 2: Phase IIa Proof-of-Concept Study

In Part 2, a Phase IIa proof-of-concept study will be conducted in patients with moderately to severely active RA experiencing an inadequate response to DMARD baseline therapy with MTX plus anti-TNF- α therapy.

Ninety patients will be randomized in a 1:2 ratio and will receive MTX plus anti-TNF- α therapy plus placebo (N=30), or MTX plus anti-TNF- α therapy plus RO7123520 810 mg/dose as adjunct therapy (N=60). As in Part 1, RO7123520 will be given as IV infusions on Days 1, 14, 28, and 56 (with patients randomized to placebo receiving IV saline), followed by the primary endpoint assessment at Week 12.

In Part 2 only, patients will undergo contrast-enhanced MRI imaging of hand/wrist, *the site to be determined by the Investigator*, to confirm disease activity at baseline and examine joint changes in patients with active RA on MTX and inadequate response to anti-TNF- α therapy. As Part 2 is the pivotal proof-of-concept part of the trial, only patients with active disease on an MRI will be enrolled.

Once the first 45 patients in Part 2 have completed the Week 12 visit, an interim analysis will be conducted with the opportunity to stop the study for futility, initiate Part 3 of the study or continue Part 2 until all 90 patients have completed the Week 12 visit.

The study will proceed to Part 3 if there are no more than one-third of the patients who received RO7123520 reporting serious study drug-related adverse events of a similar nature (e.g., laboratory abnormalities, vital sign changes, ECG changes, etc.) and if there are no other reasons to stop the study.

All patients in Part 2 will have the option of continuing to the Extension Period of the study.

Part 3: Phase IIb Dose-Ranging Study

Based on the results of an interim analysis planned during Part 2 of the study, the Phase IIb dose-ranging part of the study will begin. Applying the same criteria as in Part 2 (i.e., patients with moderately to severely active RA experiencing an inadequate response to DMARD baseline therapy with MTX plus anti-TNF- α therapy), 105 patients will be randomized 2:2:2:1 to

one of three selected RO7123520 doses, and placebo (or 5:5:5:1 if four RO7123520 doses and placebo are selected) in the range of 90 mg/dose to 720 mg/dose (e.g., 90, 180, 450 mg/dose). Final doses and the number of dose arms (3 or 4) for Part 3, along with the clarification of the sample size will be decided after analysis of safety and efficacy in the Part 2 interim analysis. Patients will receive study treatment on Days 1, 14, 28, and 56, followed by the primary endpoint assessment at Week 12.

All patients in Part 3 will have the option of continuing to the Extension Period of the study.

Extension Period

In Parts 1, 2 and 3, following the blinded, placebo-controlled 12-week study and Week 12 visit assessments an optional extension period will be conducted to collect additional safety and efficacy data up to Week 24, with the last dose being administered at Week 20. A final safety visit will occur at Week 28 (German sites: Week 36).

Patients who received active treatments in Study Parts 1, 2 or 3 will continue on the same dose of RO7123520 as they previously received in Parts 1, 2 or 3. It is planned that patients who received placebo treatment in Part 1 will receive a 360 mg dose, while patients on placebo in Parts 2 or 3 will receive an 810 mg dose of RO7123520, although a lower dose may be employed at the recommendation of the IMC/SOC.

NUMBER OF PATIENTS

A total of approximately 204 patients will take part in the study, with 9 patients in Part 1, 90 patients in Part 2 and 105 patients in Part 3.

TARGET POPULATION

Male and female patients with moderately to severely active RA who experience an inadequate response to disease-modifying anti-rheumatic drug (DMARD) therapy with MTX plus anti-TNF- α therapy for at least 3 months before randomization. This first- and second-line therapy will be continued throughout the study.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

Patients must meet the following criteria for study entry:

1. Able and willing to provide written consent by signing the Informed Consent Form (ICF), and to comply with the study protocol according to ICH and local regulations.
2. Adult men and women, *of more than* 18 years of age (inclusive).
3. Diagnosis of adult-onset RA as defined by the American College of Rheumatology (ACR) 2010 criteria, for at least 6 months before screening.
4. Moderately to severely active RA as defined by at least 4/28 tender joints and at least 4/28 swollen joints (Note: surgically treated joints cannot be counted in TJC/SJC for enrollment purposes).
5. For Part 2 only: Active synovitis and/or osteitis of the hand/wrist as determined by contrast-enhanced MRI.
6. Patients must be taking one of the following anti-TNF- α therapies: certolizumab, golimumab, etanercept, adalimumab, *infliximab* or approved biosimilars of these, given at a *recommended* and stable dose for at least 12 weeks before randomization and have

experienced in the opinion of the Investigator an inadequate response to anti-TNF- α therapy with a DAS28 \geq 3.2. Note: prior use of other anti-TNF- α therapies is allowed.

7. Patients must be taking MTX (PO, SC, or IM) for at least 12 weeks before randomization and must be on a stable dose for at least 4 weeks before randomization (5.0 to 25 mg/week). Note: The dose of MTX is expected to remain stable throughout the study and may be adjusted only for safety or intolerance reasons. Local standard-of-care should be followed for concomitant administration of folic acid.

8. Patients on glucocorticoids (\leq 10 mg/day PO prednisone or equivalent) are permitted if doses are stable within 6 weeks of planned randomization. Note: Patients should remain on stable doses of glucocorticoids throughout the duration of study unless for *medical reasons* (e.g., safety, intolerance, *RA flare, etc.*).

9. Patients taking non-steroidal anti-inflammatory drugs (NSAIDs) intermittently (e.g., up to 2-3 times weekly) for short-term relief of pain are allowed, and patients on regular NSAID use (i.e., on stable dose for \geq 4 weeks) are allowed.

Note: NSAIDs must not be taken for at least 2 days before clinical assessments in the study for patients with intermittent use of NSAIDs. If needed for symptomatic relief, paracetamol (up to 3 g/day) is permitted.

10. Negative pregnancy test at screening and baseline (women only), and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation as follows:

- Male or female patients: The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For males: men with female partners of childbearing potential or pregnant female partners, must remain abstinent or use a condom during the treatment period and up to the post-treatment follow-up visit to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
- For females: Females are eligible to participate if not pregnant and not breastfeeding. A woman of childbearing potential and female partners with childbearing potential of male patients must agree to remain abstinent (refrain from heterosexual intercourse) or use one highly effective form of contraception that results in a failure rate of $< 1\%$ per year during the treatment period and up to the post-treatment follow-up visit. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- Male and female patients should continue to use contraception after the last study drug administration until the end of relevant systemic exposure (i.e., ~ 115 days).

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from study entry:

1. Parenteral glucocorticoids administration (IM, IV) of ≥ 50 mg within 6 weeks or ≤ 50 mg within 4 weeks prior to planned randomization, or scheduled parenteral administrations during the study.
2. Joint(s) injected with intra-articular glucocorticoids within 6 weeks prior to planned randomization.
3. Active inflammatory diseases of the joints not related to RA: Gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease.
4. Systemic autoimmune disease other than RA: Systemic lupus erythematosus, Crohn's disease, ulcerative colitis, systemic scleroderma, inflammatory myopathy, mixed forms of connective tissue inflammatory diseases.
5. Juvenile idiopathic arthritis or juvenile RA and/or RA developed before the age of 16.
6. Active fibromyalgia that makes appropriate RA disease activity challenging for the Investigator.
7. RA patients functional status class IV according to the ACR 1991 criteria (i.e., largely or wholly incapacitated permitting little or no self-care, such as being bedridden or confined to wheelchair).
8. Patients with severe chronic or recurrent viral, bacterial, parasitic or fungal infections.
9. History of active hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection.
10. Any identified confirmed congenital or acquired immunodeficiency.
11. Abnormal laboratory values:
 - Hemoglobin level is less than 80 g/L.
 - Leucocyte level is less than 2.5×10^9 /L.
 - Absolute neutrophil count is less than 1.0×10^9 /L.
 - Thrombocyte level is less than 75×10^9 /L.
12. Laboratory test results for liver function meeting criteria for marked abnormality (ULN: upper limit of normal): Alkaline phosphatase: $> 3 \times$ ULN; aspartate aminotransferase: $> 3 \times$ ULN; alanine aminotransferase: $> 3 \times$ ULN; γ -glutamyl transferase: $> 3 \times$ ULN.
13. Other unstable somatic diseases apart from RA that can increase the probability of adverse events during the study, mask, enhance or alter the symptoms of RA or cause clinical or laboratory symptoms similar to that of RA.
14. Major surgery within 28 days prior to randomization, or *planned* major surgery (e.g., elective joint replacement surgery) during the trial.
15. Any mental disorder, including major depressive disorder and/or suicidal thoughts in anamnesis that can, in the Investigator's opinion, create a risk for the patient or influence the patient's ability to follow the study protocol.
16. Myocardial infarction within less than 6 months prior to participation in the study.
17. Severe central or peripheral nervous system diseases.
18. Chronic drug or alcohol abuse.
19. Known hypersensitivity to any components of the medications used in the study.
20. Acute forms of any infectious diseases or history of chronic infections with severe clinical manifestations that would increase risk in participation of trial in the opinion of the Investigator.

21. Presence of malignant neoplasm, with the exception of adequately treated basal cell carcinoma and cervical carcinoma in situ and any malignancy with complete remission of more than 5 years.
22. Simultaneous participation in any other clinical trial, as well as former participation in other clinical trials within 3 months before this study initiation; and previous study drug administration in this study.
23. German sites: Patients who are institutionalized due to regulatory or juridical order.
24. German sites: Patients who are occupationally or medically dependent on the Sponsor, the Investigator, or the medical site.

LENGTH OF STUDY

The total duration of the study for each patient will be up to 32 weeks (German sites: 40 weeks) divided as follows:

- Screening: Up to 4 weeks
- Study treatment duration: Days 1 up to 84 (Baseline to Week 12)
- Study treatment duration including Extension Period: Days 1 up to 168 (Baseline to Week 24)
- Safety Follow-up: Day 112 (Week 16). German sites: Day 112 (Week 16) and Day 168 (Week 24).
- Safety Follow-up including Extension Period: Day 196 (Week 28). German sites: Day 196 (Week 28) and Day 252 (Week 36).

Only Patients in Study Part 1 will be required to stay overnight at the Study Center after each dose of study treatment up to and including the Week 8 administration. The first 15 patients in Part 2 will be required to stay overnight at the Study Center after the first dose of study treatment, or alternatively, two visits within 24 hours post-dose can be made by an ambulatory at-home visiting nurse to perform assessments as described in the SoA.

END OF STUDY

The end of the study is defined as the date when the last patient last observation (LPLO) occurs. LPLO is expected to occur 28 weeks (German sites: 36 weeks) after the last patient is enrolled.

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of adverse events, including targeted adverse events, number of participants with SAEs, treatment-related SAEs, SAEs leading to discontinuation, treatment-related AEs, or AEs leading to discontinuation
- Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- ECGs
- Vital signs
- Assessment of bone remodeling and cartilage markers (e.g., CTX-I, PINP and osteocalcin)
- Assessment of blood cell markers (including, but not limited to, CD4, CD8, CD19, CD16/56, CD3, CD45, CD14)
- Anti-drug antibodies (ADA)
- Bone mineral density lumbar spine L1-L4 by dual energy X-ray absorptiometry (DEXA) scans, which involves the exposure of a very small amount of X-ray radiation around one to six microSievert (μ Sv).

PHARMACOKINETIC OUTCOME MEASURES

RO7123520 serum and synovial fluid concentration data will be pooled with corresponding data from other studies (e.g., SDP051-001) for population PK and PK/PD modelling of the exposure versus response relationship.

EFFICACY OUTCOME MEASURES

The efficacy outcome measures for this study are as follows:

Primary Outcome Measure:

- Proportion of patients achieving an ACR50 response at Week 12

Secondary Outcome Measures:

- Change from baseline in CDAI Score at Week 12
- Change from baseline in DAS28 at Week 12
- Proportion of patients achieving DAS28 remission at Week 12
- Proportion of patients achieving CDAI remission at Week 12
- Proportion of patients achieving an ACR20 response at Week 12
- Proportion of patients achieving an ACR70 response at Week 12
- Simple Disease Activity Index (SDAI) Score at Week 12
- Change from baseline in the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12

EXPLORATORY OUTCOME MEASURES

The exploratory outcome measures for this study include but are not limited to the following:

- Proportion of patients achieving an ACR50 response at Week 24
- CDAI Score at Week 24
- DAS28 at Week 24
- Proportion of patients achieving DAS28 remission at Week 24
- Proportion of patients achieving CDAI remission at Week 24
- Proportion of patients achieving an ACR20 response at Week 24
- Proportion of patients achieving an ACR70 response at Week 24
- Proportion of patients achieving a mACR50 response at Weeks 12 and 24
- Proportion of patients achieving a mACR20 response at Weeks 12 and 24
- Proportion of patients achieving a mACR70 response at Weeks 12 and 24
- SDAI Score at Week 24
- Change from baseline in the Stanford HAQ-DI at Week 24
- Change from baseline in Short-form 36 health questionnaire Physical and Mental Health component scores (SF36V2 standard recall) at Weeks 12 and 24
- Change from baseline in Brief Fatigue Inventory (BFI) total and item scores at Weeks 12 and 24
- Change from baseline in patient global assessment of disease activity at Weeks 12 and 24
- Change from baseline in patient global assessment of pain at Weeks 12 and 24
- Change from baseline in Cad-11 synovium level and in synovial fluid *and blood* soluble Cad-11 concentration at Weeks 12 and 24
- Change from baseline of the PD biomarkers (e.g., bone remodeling and cartilage markers) at Weeks 12 and 24
- Change from baseline in synovitis, osteitis, joint erosions, cartilage loss, bone marrow edema, total damage and total inflammation at Weeks 12 and 24 evaluated by rheumatoid arthritis MRI score (RAMRIS) of the hand/wrist.

Biomarkers (non-DNA)

Roche Research Biosample Repository (RBR) non-DNA specimen (s) will be taken from consenting subjects at the timepoints specified in the Schedule of Assessments (SoA).

- Residual synovial tissue and fluid from any patient who consents to their collection and to store in RBR post-study
- Plasma, serum, to assess for biomarkers
- Blood for DNA and RNA extraction to assess for biomarkers

These specimen(s) may be stored for up to 15 years after the end of study.

Biomarkers (DNA)

All subjects who have been enrolled in the study will be asked to donate an optional DNA specimen for pharmacogenetic and genetic research. RBR DNA sampling will involve taking a blood sample at the timepoints specified in the SoA. These specimen(s) may be stored for up to 15 years after the end of study.

INVESTIGATIONAL MEDICINAL PRODUCT(S)

Test Product

RO7123520 drug product (30 mg/mL) will be provided in single-use, 6 mL vials.

For IV infusion, RO7123520 concentrate for solution for infusion should be diluted in 0.9% (w/v) sodium chloride solution prior to administration.

Placebo

Patients randomized to placebo will receive IV infusions of saline alone, therefore no actual matching placebo will be provided. It is not possible to differentiate between the IV bags which contain only saline and those which have RO7123520 added.

PROCEDURES

Informed consent will be obtained prior to any study-specific procedures. Following eligibility at screening and the confirmation at baseline, patients will be enrolled into the study. The assessments will be conducted at times as indicated in the SoA.

Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the SoA.

The exact assessments may vary by specific visit date and the sequence will be standardized as follows (at visits as specified in the SOA):

1. Patients will complete health outcomes assessments using an electronic ePRO device, specific to each study visit day/week.
 - SF36v2
 - HAQ-DI
 - BFI
 - PtPA (pain VAS)
 - PtGA (Global Assessment of disease activity VAS)
2. Laboratory samples for safety, efficacy, PD and PK; must be drawn after patient self-assessments are completed, at least 30 min before Investigator assessments or at any time after nurse/Investigator assessments but prior to study drug infusion.

Note: providing all listed restrictions are met, the lab samples can be collected before or after the joint count is performed.
3. Investigator assessments:
 - Joint counts
 - Physician's global assessment of disease activity VAS, safety assessments (adverse events, vital signs, concomitant medications, review of laboratory data)
4. RO7123520/placebo infusion
5. Post-dose vital signs, post-dose PK (at the visits scheduled), adverse events.

Patients who complete the study or discontinue from the study early will be asked to return to the clinic 8 weeks (German sites: 8 and 16 weeks) after the last dose of study drug for a follow-up visit.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary analysis will include all patients in the efficacy analysis population, with patients grouped according to the treatment and dose assigned at randomization.

The primary efficacy endpoint to demonstrate the proof of concept of RO7123520 is the proportion of patients achieving an ACR50 response at Week 12 using RO7123520 as adjunct therapy to MTX+anti-TNF- α compared to MTX+anti-TNF- α plus placebo.

An ACR50 response is defined by achieving an improvement of $\geq 50\%$ compared to baseline in the American College of Rheumatology (ACR) core set of outcome measures in both SJC and TJC as well as in 3 out of 5 additional parameters: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain (PtPA), HAQ-DI, and acute phase reactant (CRP will be used as the ACR APR in this study).

Patients who withdraw from the study prior to the Week 12 ACR assessment, and all patients in whom the Week 12 ACR50 response cannot be determined for any reason, will be considered non-responders for the summaries of ACR50.

The proportion of patients achieving an ACR50 response at Week 12 will be summarized descriptively by treatment/dose arm.

SAFETY ANALYSES

All safety analyses will be based on the safety analysis population and reported by the treatment group and dose actually received.

- Adverse events will be summarized by mapped term and appropriate thesaurus level. Incidence, nature and severity of adverse events, including targeted adverse events, number of participants with serious adverse events (SAEs), treatment-related SAEs, SAEs leading to discontinuation, treatment-related AEs, or AEs leading to discontinuation will be tabulated by treatment group and dose.
- Clinical Laboratory Test Results will be presented by individual listings with flagging of values outside the normal ranges.
- Vital signs and weight data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.
- ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.
- Concomitant medications will be presented in summary tables and listings.

PHARMACOKINETIC ANALYSES

RO7123520 concentration data will be pooled with data from other studies (e.g., SDP051-001) for population PK and PK/PD modelling. The methods and results of that population modelling will be reported separately.

EXPLORATORY ANALYSES

- The proportion of mACR20/mACR50/mACR70 responders at Week 12 and Week 24 will be summarized descriptively using the efficacy analysis population.
- The change from Baseline in SF-36v2 mental component score (MCS) and physical component score (PCS) at Week 12 and Week 24 will be summarized descriptively by treatment/dose arm using the efficacy analysis population.
- The change from Baseline in BFI items 2, 3 and 4, as well as total score will be summarized descriptively at Week 12 and Week 24 by treatment/dose arm using the efficacy analysis population.
- The PtGA VAS and PGA VAS will be presented individually to describe, respectively, the patient and physician global assessment of disease activity changes from baseline at Week 12 and Week 24 using the efficacy analysis population.

The PtPA VAS change from baseline at Week 12 and Week 24 will also be presented using the efficacy analysis population.

PtGA, PGA and PtPA VAS changes from baseline will be summarized descriptively.

- The potentially prognostic and disease severity biomarkers (MBDA and CTX-II) will be summarized descriptively at Baseline by treatment/dose arm. In addition, the synovium cadherin-11 *data*, synovial fluid *and* blood soluble cadherin-11 data will be summarized descriptively by visit and treatment/dose arm. Those biomarkers will be summarized using the efficacy analysis population.

The relationship between the potentially prognostic and disease severity biomarkers and efficacy endpoints will also be analyzed and reported descriptively.

- Bone remodeling and cartilage markers (including but not limited to CTX-1, PINP and osteocalcin) will be summarized descriptively by visit and treatment/dose arm. Those biomarkers will be summarized using the efficacy analysis population.

The relationship between the markers mentioned above and efficacy endpoints will also be analyzed and reported descriptively.

- Safety biomarkers (T cells, B cells, NK cells, granulocyte and monocyte markers) will be summarized descriptively by visit and treatment/dose arm using the safety analysis population.
- Disease activity as assessed by MRI (Part 2 only):

The OMERACT RA MRI scoring system (RAMRIS) will be used for the evaluation of inflammatory and destructive changes in RA hands and wrists at baseline, Week 12 and Week 24. The change from baseline in synovitis, osteitis, bone erosions, cartilage loss, bone marrow edema, total damage and total inflammation will be summarized descriptively by visit and treatment arm using the efficacy analysis population.

SAMPLE SIZE JUSTIFICATION

Part 1:

No formal sample size estimation was performed for Part 1 of the study. A total of 9 patients (6 on the RO7123520 arm and 3 on the placebo arm) is deemed sufficient to provide initial safety information on RO7123520 in RA patients.

Part 2:

A total of 90 patients will be randomized 2:1 to either the RO7123520 or placebo arm. The probability of observing a difference of at least 15% between the RO7123520 and placebo Week 12 ACR50 response rates is approximately 0.73, assuming that the *true* ACR50 response rate on placebo is 15% and 35% on RO7123520. With 60 patients receiving RO7123520 810 mg, there is at least a 95% chance of observing an AE with true incidence of $\geq 5\%$. This number of Ninety patients will therefore give a reasonable assessment of the safety and efficacy of RO7123520 before progressing to Part 3.

Part 3:

Following the decision to initiate Part 3 at the interim analysis of Part 2 of the study or after the end of Part 2 (when all 90 patients have reached the Week 12 visit) (Section 6.9), 105 patients will be randomized 2:2:2:1 to one of 3 selected RO7123520 doses, and placebo (or 5:5:5:1 if four RO7123520 doses and placebo are selected).

The total sample size for the combined Study Parts 1, 2 and 3 will be 204 patients (either 60, 30, 30, 30 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 48 receiving placebo, or 60, 25, 25, 25, 25 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 38 receiving placebo). This provides approximately 80% power of observing a positive dose response curve with a maximum effect of RO7123520 compared to placebo of -8.0 in change from baseline in CDAI score at Week 12 (placebo change from baseline in CDAI is assumed to be -10.0, with a common standard deviation of 15.0), allowing for a 10% drop-out rate and using a two-sided alpha level of 0.1.

If conflicting results are observed from Study Part 2 of the study between the change from baseline in CDAI at Week 12 endpoint and ACR50 response at Week 12 endpoint, then the following sample size for Part 3 will be undertaken and the dose-response analysis will be based on ACR50 at Week 12:

A total sample size of 150 patients will be recruited into part 3 of the study. Therefore the total sample size for the combined Study Parts 1, 2 and 3 will be 249 patients (either 60, 45, 45, 45 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 48 receiving placebo, or 60, 36, 36, 36, 36 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 39 receiving placebo), which provides approximately 80% power of observing a positive dose response curve using a two-sided alpha level of 0.1, and assuming a placebo ACR50 response of 15% and active RO7123520 response of 35%, i.e., a delta effect size of 20%.

Interim Analyses

An interim analysis of the primary efficacy outcome measure (ACR50 at Week 12) will be carried out after the first 50% of the patients within Part 2 of the study have completed their Week 12 assessment visit. The data will be reviewed by the IMC and SOC.

The difference in ACR50 response rate at Week 12 between the RO7123520 810 mg dose group and the placebo group will be compared descriptively. If no difference between the treatment arms is observed for ACR50 (i.e., the difference is $\leq 0\%$) then, the study may be stopped for futility. If a positive difference is observed then, the Sponsor will determine whether to start Part 3 of the study at this point (also continuing Part 2 recruitment until completion) or wait until all of the Part 2 patients have been recruited and have completed the Week 12 visit,

where the decision will be revisited.

Once all of the patients in Study Part 3 have completed their Week 12 visit, a data snapshot will be taken for the purpose of the dose-response analysis. The study will not be modified at this point and will continue until all patients have completed the final follow-up visit.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

LIST OF PROHIBITED MEDICATIONS

The following medications are prohibited after randomization:

- Live vaccines, including herpes zoster vaccination. Non-live seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed.
- Any biologic therapy such as anti-IL-1, anti-IL-6, or T-cell or B-cell targeted therapies for any indication.
- Any interferon therapy for any indication.
- Any parenteral corticosteroid administered by IV injection.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse events
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BFI	Brief Fatigue Inventory
BP	Blood pressure
CDAI	Clinical Disease Activity Index
CL	Clearance
CL/F	Apparent clearance
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTX-II	Collagen type II C-telopeptide
DAS28	Disease Activity Score
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ELISA	<i>Enzyme-linked immunosorbent assay</i>
ePRO	Electronic patient-reported outcome
ESF	Eligibility Screening Form
EU	European Commission
FDA	Food and Drug Administration
HAQ-DI	Stanford Health Assessment Questionnaire Disability Index
HBsAG	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCV	Hepatitis C
HDL	High-density lipoproteins
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

Abbreviation	Definition
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IUD	Intrauterine Device
IV	Intravenous
IxRS	Interactive (voice/web) response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LPLV	Last patient, last visit
MBDA	Multi-biomarker disease activity
MRI	Magnetic resonance imaging
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
NGS	Next Generation Sequencing
NOAEL	No-observed-adverse-effect level
OTC	Over-the-counter
PD	Pharmacodynamic
PGA	Physician Global Assessment of Disease Activity
PINP	Aminoterminal propeptide of type I collagen
PK	Pharmacokinetic
PRO	Patient-reported outcome
PT	Prothrombin time
PtGA	Patient Global Assessment of Disease Activity
PtPA	Patient Assessment of Pain
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate

Abbreviation	Definition
QTcF	QT corrected for heart rate using the Fridericia correction factor
RA	Rheumatoid arthritis
RBC	Red blood cell
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RR	RR interval
SAD	Single-Ascending Dose
SAE	Serious Adverse Event
SD	Single dose
SDAI	Simple Disease Activity Index
SoA	Schedule of Assessments
SOC	Scientific Oversight Committee
SF-36v2	Short-form Health Survey Version 2
SUSAR	Suspected unexpected serious adverse reactions
TNF-α	Tumor necrosis factor- α
TQT	Thorough QT
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
V_z	Volume of distribution
VAS	Visual analogue scale
WBC	White blood cell
WGS	Whole genome sequencing

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks synovial joints, resulting in joint damage with loss of function and mobility. Current first-line treatment regimens include the use of corticosteroids alone or in combination with conventional disease-modifying anti-rheumatic drugs (cDMARDs), most commonly methotrexate. However, only approximately 50% of RA patients experience a 50% improvement in clinical signs and symptoms, with the majority of patients demonstrating only a partial response to treatment ([Voll and Kalden 2005](#)). As second-line treatments, biologic agents (including monoclonal antibodies, mostly directed against TNF- α and its receptors, so-called biological DMARDs, bDMARDs) are added in order to control the disease with the target to achieve low disease activity (LDA) or even remission.

Synovial fibroblasts are the major non-immune cell population of the inflamed RA joint and are thought to play a significant role in cartilage destruction and in tissue inflammation. Therefore, targeting synovial fibroblasts comprises an attractive and novel non-immunosuppressive approach for interrupting pathophysiology of the RA joint, particularly if combined with existing DMARDs and biologics as an adjunctive approach to increase efficacy without increasing immunosuppressive side-effects.

Cadherin-11 (Cad-11) is a classical cadherin adhesion molecule that mediates homophilic cell-to-cell adhesion. Cad-11 is selectively expressed in synovial fibroblasts, and plays an important role in the pathogenesis of inflammatory arthritis ([Lee et al 2007](#)). There is mounting evidence from preclinical in vitro and in vivo studies which suggest that Cad-11-mediated activation of synovial fibroblasts results in their production of pro-inflammatory factors. This suggests that Cad-11 may be an important modulator of inflammation and cytokine release by synovial fibroblasts. In fact, Cad-11 engagement was shown to synergize with TNF- α to markedly increase cytokine (i.e., IL-6) production, which in contrast was decreased in ankle joints from Cad-11-deficient mice compared with wild-type mice with inflammatory arthritis ([Chang et al 2011](#)). These and additional published findings suggest that Cad-11 plays a critical role in evoking synovial fibroblast inflammatory factors that contribute to RA ([Chang et al 2011](#)).

Further supportive evidence for Cad-11 as a potential therapeutic target in RA is that expression of Cad-11 in fibroblasts is restricted to the site of active inflammation. There is little to no general, systemic fibroblast protein expression of Cad-11 ([Valencia et al 2004](#)); therefore, blocking Cad-11 has the potential to be a targeted and local approach with limited side-effects expected due to very limited Cad-11 interference outside of inflamed joints in RA.

Selectively blocking upregulated Cad-11 function in inflamed tissues using a non-immunosuppressive strategy might represent a potentially effective and novel

therapy for the treatment of patients with moderately to severely active RA and an inadequate response to anti-TNF- α therapy.

RO7123520 is a novel, humanized IgG4 monoclonal antibody that specifically binds to the first extracellular (EC1) domain of Cad-11. It is being investigated for the treatment of moderate to severe RA as an adjunctive treatment to biologic and non-biologic DMARDs.

1.2 BACKGROUND ON RO7123520

See the [RO7123520 Investigator's Brochure](#) for details on non-clinical and clinical studies.

1.2.1 Previous Non-Clinical Studies

In vitro studies to evaluate the potential beneficial effects of RO7123520 in RA were conducted in human synovial fibroblasts. Exposure to RO7123520 in vitro significantly reduced both matrix metalloproteinase-3 (MMP-3) levels and invasion into a Matrigel-coated membrane at drug concentrations as low as 0.3 μ g/mL.

In vivo studies in a relevant murine model of RA involving synovitis, the KBN model, showed that RO7123520 reduced swelling of joints and joint destruction at 10 mg/kg and resulted in a trend towards reduced joint swelling at 3 mg/kg. The reduction of joint swelling by RO7123520 was correlated with a reduction in the levels of some cytokines implicated in RA pathogenesis in humans.

Among cadherins, RO7123520 binds preferentially to Cad-11, with an EC₅₀ that is at least 500-fold lower than for other closely-related cadherins.

RO7123520 is considered unlikely to produce adverse effects on nervous system, cardiovascular system, or respiratory system function in humans, based on results of safety pharmacology evaluations. RO7123520 did not adversely affect respiratory system function or functional observational battery (FOB) test results in rats given single intravenous (IV) doses at up to 200 mg/kg, and did not affect electrocardiograms (ECGs) in cynomolgus monkeys given weekly IV doses for 4 weeks at up to 200 mg/kg.

Single- and repeat-dose IV toxicity studies in mice, rats, and cynomolgus monkeys included evaluation of systemic exposure (toxicokinetics), immunogenicity (anti-drug antibodies [ADA]), and reversibility of effects (recovery). No adverse effects were observed at any dose level in the rat and cynomolgus monkey single-dose and 4- or 26-week toxicity studies following single or once weekly IV administration of RO7123520 up to the maximum feasible dose of 200 mg/kg. The no-observed-adverse-effect level (NOAEL) for these studies in each species was considered to be 200 mg/kg. In the 2-week single and 4-week IV toxicity studies in mice, death was reported in three mice. It occurred shortly after administration of the third or fourth weekly dose at \geq 30 mg/kg, and was considered to be immune-mediated anaphylaxis triggered by a response against the

humanized RO7123520. Based on these findings, the NOAEL was considered to be 10 mg/kg in mice.

The pharmacokinetics and toxicokinetics of RO7123520 were studied after single IV bolus doses in Sprague-Dawley rats and cynomolgus monkeys and after repeated weekly IV bolus doses in CD-1 mice, Sprague-Dawley rats, and cynomolgus monkeys. Weekly IV administration of RO7123520 produced substantial, long-lasting serum concentrations in all species. In each species, the volume of distribution (V_z), clearance (CL), and half-life ($t_{1/2}$) generally were similar in both sexes. V_z approximated or was slightly larger than the serum volume (40-60 mL/kg), which is typical for monoclonal antibodies. RO7123520 was cleared slowly from the serum with $t_{1/2}$ ranging from ~2 to 16 days across species. Clearance did not change substantially with dose level in rats and cynomolgus monkeys, but increased with dose level in mice, likely a result of a robust anti-drug antibody (ADA) response at the higher dose levels.

For more details on nonclinical studies see the [RO7123520 Investigator's Brochure](#).

1.2.2 Previous Clinical Studies

RO7123520 has been administered to healthy subjects in one clinical Phase 1 study ([SDP051-001](#)). Study SDP051-001 was a randomized, double-blind, placebo-controlled, single-ascending dose (SAD) design in which healthy male and female subjects received single IV doses of either RO7123520 or placebo. The primary objectives were to establish the pharmacokinetics (PK), safety and tolerability of single IV doses of RO7123520. Subjects underwent PK, pharmacodynamics (PD) and safety assessments at regular intervals up to 84 days after dosing. A total of 35 eligible subjects were enrolled into the study in five cohorts. Within each cohort, 5 subjects received RO7123520 and 2 subjects received placebo. Study drug was administered as a 1-hour IV infusion and the five RO7123520 doses tested were 0.1, 0.3, 1, 3, and 10 mg/kg of body weight (i.e., average actual doses 8, 22, 79, 243 and 847 mg, respectively).

RO7123520 pharmacokinetics after administration of a single IV dose were linear across the dose range tested. RO7123520 peak and total exposure increased in a dose-proportional manner. Volume of distribution was approximately 6.5 L, while clearance was approximately 0.008 L/h. The apparent terminal half-life was approximately 23 days on average.

Single IV doses of RO7123520 up to 10 mg/kg (average actual dose 847 mg) were tolerated similarly to placebo by healthy subjects. There were no deaths, serious adverse events (SAEs), or discontinuations from the study because of adverse events (AEs). No dose-limiting AEs were identified.

There were a total of 45 treatment-emergent AEs reported for 19 of 25 (76.0%) RO7123520-administered and 6 of 10 (60.0%) placebo-administered subjects. The most frequently reported treatment-emergent AEs during the study were contact dermatitis

and headache. Contact dermatitis was reported in 6 of 25 (24.0%) RO7123520 –administered subjects and in no placebo-administered subjects. Contact dermatitis was attributed to ECG patches in four subjects and poison ivy in one subject. One additional case of application site erythema due to foam antiseptic was reported by a subject who received 0.1 mg/kg RO7123520. Headache was reported in 4 of 25 (16.0%) RO7123520-administered subjects and in no placebo-administered subjects. All 4 reported episodes of headache were mild and resolved without treatment. All other treatment-emergent AEs were reported in two or fewer individuals, and showed no apparent relationship to treatment.

The immunogenic potential of RO7123520 was assessed by measurement of anti-RO7123520 drug antibodies (ADA) before, and 2, 4, 8, and 12 weeks after study drug dosing. One of 25 subjects who received RO7123520 developed ADAs. This subject was negative prior to receiving a 0.1 mg/kg dose of RO7123520 but was positive for ADA at all post-dose assessments.

Four additional subjects (one placebo subject, one subject at 0.1 mg/kg, and two subjects at 0.3 mg/kg dose) tested positive for ADAs at baseline (pre-dose) as well as at all post-dose visits.

For more details on the previous clinical study, see the [RO7123520 Investigator's Brochure](#).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

RO7123520 is a novel anti-cadherin-11 monoclonal antibody. Cadherin-11 (Cad-11) is a classical cadherin adhesion molecule that mediates homophilic cell-to-cell adhesion. Recent studies have demonstrated that Cad-11 is selectively expressed in synovial fibroblasts and plays an important role in the pathogenesis of inflammatory arthritis ([Lee et al 2007](#)). Selectively blocking upregulated Cad-11 function in inflamed tissues might represent a potentially effective and novel therapy for the treatment of patients with moderately to severely active RA and an inadequate response to anti-TNF- α therapy.

The principal aim of the study is to establish the safety, tolerability and efficacy profile of RO7123520 when administered to patients with RA who have had an inadequate response (IR) to at least one biologic anti-TNF- α therapy (RA TNF-IR patients) and who are also taking background cDMARDs (i.e., with methotrexate [MTX]). However, because this is an early study in the clinical development of a compound with a novel mechanism of action, there is a need to profile the pharmacological effects of RO7123520 treatment. The study is, therefore, also intended to characterize the effects of RO7123520 through appraisal of a variety of relevant pharmacodynamic measures and biomarkers, and to establish the relationship between drug exposure and any treatment response. Data from this study are intended to inform the future development potential for RO7123520 in RA TNF-IR patients.

1.3.2 Benefit-Risk Assessment

Rheumatoid arthritis is a chronic systemic autoimmune disease characterized by progressive damage to synovial joints. Although there are a number of approved, effective treatments for RA available, many patients nevertheless experience significant ongoing disease activity. This study will recruit patients with RA who have had an inadequate response to current first- and second-line standard-of-care treatments, a group for whom switching to another immunosuppressive/immunomodulatory biologic therapy with a different mode of action is recommended in order to achieve better treatment response (e.g., American College of Rheumatology [ACR] guidelines, [Singh et al. 2016](#); European League Against Rheumatism [EULAR] guidelines, [Smolen et al 2014](#)). The available data on Cad-11 and preclinical data on RO7123520 provide a reasonable expectation that RO7123520 treatment might provide benefit on the signs and symptoms of RA and ameliorate joint destruction. However, this is the first study to test the effects of a therapy targeting Cad-11; there are no clinical data to prove that individuals will derive any benefit from RO7123520 treatment. Furthermore, as this is a placebo-controlled study, patients who are randomized to placebo will not derive direct benefit from participation in the blinded parts of the study.

The risks of study participation are primarily those associated with adverse reactions to the study drug, although there may also be some discomfort from collection of blood and synovial fluid samples and other study procedures. Participants in the optional synovial biopsy sub-study will also have additional discomfort and risk of sequelae from the biopsy procedure.

Study BP39261 is the second study involving dosing of RO7123520 to humans but the first involving dosing in patients with RA. Data from a previously completed clinical study performed in healthy subjects ([SDP051-001](#)) show an acceptable tolerability profile over the dose range tested. There were no notable safety findings from single doses up to 10 mg/kg (average actual dose 847 mg), indicating there are no acute safety risks associated with RO7123520 dosing or the mechanism of action. Similarly, mice lacking Cad-11 (“knockout” mice) have a largely normal phenotype, suggesting that there are no serious safety concerns associated with depletion of Cad-11. Therefore, repeat-dose non-clinical toxicology studies are the principal guide to potential adverse drug reactions from long-term dosing with RO7123520. Those studies did not reveal any findings of particular concern for dosing patients at the proposed doses of up to 810 mg for up to 24 weeks. The preclinical safety profile in repeat-dose GLP toxicology studies in rats and cynomolgus monkeys, and the associated margins versus NOAEL exposures, support the initiation of long-term clinical studies. Using model-predicted human exposure from 810 mg dosing, the exposure margins based on NOAEL exposures in the 26-week rat and monkey studies, were 7-fold in rat and 9-fold in monkey with AUC-based safety margins, and 28-fold in rat and 54-fold in monkey with C_{max} -based safety margins.

The potential for clinically relevant drug-drug interactions between RO7123520 and other concomitant medications is believed to be minimal. There are no data available on the use of RO7123520 with MTX or biologic anti-TNF- α therapies, but clinically important drug-drug interactions are not anticipated. There is limited potential for pharmacokinetic drug-drug interactions between monoclonal antibodies and other therapies, and because the mode of action of RO7123520 is distinct from those of MTX and anti-TNF- α therapies, clinically important pharmacodynamic drug-drug interactions are also not anticipated. In particular, because RO7123520 does not appear to have direct effects on the immune system, there is believed to be limited risk of clinically important immunosuppression from RO7123520 treatment, even when used in conjunction with immunosuppressive biological anti-TNF- α therapies.

All study participants will undergo safety assessments at intervals throughout the study, including measurements of bone density and careful assessments of the skin (Section 5.1.2). No test article-related effects were observed in GLP toxicology studies in rats and monkeys, and hence do not indicate a requirement for specific safety monitoring measures. Non-clinical studies and available clinical data reveal no evidence suggesting a risk of clinically important immunosuppression and special measures to monitor immune function are not considered to be necessary.

Synovial fluid sampling, also termed arthrocentesis or joint aspiration, is a standard, minimally invasive technique that can be performed by rheumatologists in a clinic setting with minimal risk of complications or sequelae. While not routinely performed for management of patients in clinical practice, sampling in the context of a clinical study can be justified as an investigational tool in order to allow assessment of target engagement and local pharmacodynamic effects.

Patients who choose to participate in the optional synovial biopsy will have biopsies performed at the beginning and end of the study. Synovial biopsies are minimally invasive and are commonly used in clinical practice for diagnostic purposes. Closed-needle processes are safely performed in a clinic setting, however they may be uncomfortable, require use of anesthetic and may result in post-procedural soreness. There is also a risk of sequelae from the biopsy procedure such as pain, bleeding, infection or damage to the joint, or surrounding nerves or blood vessels. Therefore, biopsies will only be performed on consenting individuals at selected study centers with experience of performing biopsies, i.e., centers where biopsies are routinely performed by experienced practitioners.

In summary, non-clinical data provide the necessary rationale that RO7123520 may provide a treatment benefit for patients with RA. The safety findings from the Phase 1 study (Study SDP051-001) support the use of RO7123520 in patients with RA. Where theoretical risks from RA treatment have been identified, appropriate clinical safety monitoring measures are implemented. Hence, the risks to participants in this study are considered acceptable.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is:

- To assess the safety, tolerability and efficacy of RO7123520 as adjunctive treatment with MTX and anti-TNF- α therapy in patients with moderately to severely active RA with an anti-TNF- α inadequate response (Study Parts 1,2,3).

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To assess the dose-ranging efficacy of RO7123520 (Study Part 3).
- To assess the exposure versus response relationship and immunogenicity of RO7123520 (Study Parts 1,2,3).

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore biomarker changes in serum, plasma, urine, synovial fluid and synovial tissue (Study Parts 1,2,3).
- To explore biomarker changes and their relationship with clinical efficacy endpoints (Study Parts 1,2,3).
- To explore joint changes by magnetic resonance imaging (MRI; Study Part 2).

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a Phase IIa/b double-blind, placebo-controlled, randomized, parallel group, global multicenter study to evaluate the safety and efficacy of RO7123520 as adjunctive therapy in patients with RA who are inadequately responding to standard-of-care (MTX and anti-TNF- α therapy).

Patients with moderately to severely active RA will be recruited if they experience an inadequate response to DMARD therapy with MTX plus anti-TNF- α therapy for at least 3 months before randomization. This first- and second-line therapy will be continued throughout the study. The MTX and anti-TNF- α dose and product should not be changed during the study, unless for safety or intolerance reasons, until the primary endpoint assessment. All patients will receive concomitant folic acid supplementation as per local standard-of-care. The randomization will be stratified by the patient's duration of prior anti-TNF- α therapy (3-12 months vs > 12 months) for Study Parts 2 and 3.

The study will be conducted in three parts. A final safety visit will occur 8 weeks (German sites: 16 weeks) after the patient's final study dose, regardless of the study part of the last received dose. See [Figure 1](#) for an overview of the study design.

3.1.1.1 Part 1: Safety Cohort

A safety cohort of patients with moderately to severely active RA will be treated with RO7123520 as adjunctive therapy with MTX and anti-TNF- α therapy. Nine patients will be randomized in a 1:2 ratio and will receive placebo (N=3), or RO7123520 360 mg/dose as adjunct treatment (N=6). In Part 1 dosing will be staggered and no more than two patients will be dosed on any given day. Four doses of RO7123520/placebo will be given as IV infusions on Days 1, 14, 28 and 56 (see [Section 3.2.2](#) for the rationale for dosage selection). A double-blind design will be used with placebo-administered patients receiving IV infusions of saline only. When all of the nine patients in Part 1 have reached the Day 42 (Week 6) visit, i.e., two weeks after the 3rd dose administration, an Internal Monitoring Committee (IMC) along with an external Scientific Oversight Committee (SOC) will perform a safety review of unblinded data ([Section 3.1.2](#)). The SOC and the IMC will advise the clinical trial team of their opinion on the study conduct.

The study will proceed to Part 2 if there are no more than one-third of the patients who received RO7123520 reporting serious study drug-related adverse events of a similar nature (e.g., laboratory abnormalities, vital sign changes, ECG changes, etc.) or if there are no other reasons to stop the study (see [Section 4.7.2](#)).

All patients in Part 1 will have the option of continuing to the Extension Period of the study ([Section 3.1.1.4](#)).

3.1.1.2 Part 2: Phase IIa Proof-of-Concept Study

In Part 2, a Phase IIa proof-of-concept study will be conducted in patients with moderately to severely active RA experiencing an inadequate response to DMARD baseline therapy with MTX plus anti-TNF- α therapy.

Ninety patients will be randomized in a 1:2 ratio and will receive MTX plus anti-TNF- α therapy plus placebo (N=30), or MTX plus anti-TNF- α plus RO7123520 810 mg/dose as adjunct therapy (N=60) (see [Section 3.2.2](#)). As in Part 1, RO7123520 will be given as IV infusions on Days 1, 14, 28, and 56 (with patients randomized to placebo receiving IV saline), followed by the primary endpoint assessment at Week 12.

In Part 2 only, patients will undergo contrast-enhanced MRI imaging of the hand/wrist, *the site to be determined by the Investigator*, to confirm disease activity at baseline and examine joint changes in patients with active RA on MTX and inadequate response to anti-TNF- α therapy. As Part 2 is the pivotal proof-of-concept part of the trial, only patients with active RA disease on an MRI will be enrolled. The MRI readings will be

conducted centrally by a blinded reader, and the Imaging CRO will confirm and communicate patient eligibility in Study Part 2 to the Investigator(s).

Once the first 45 patients in Part 2 have completed the Week 12 visit, an interim analysis will be conducted (Section 6.9) with the opportunity to stop the study for futility, initiate Part 3 of the study (Section 3.1.1.3) or continue Part 2 until all 90 patients have completed the Week 12 visit.

The study will proceed to Part 3 if there are no more than one-third of the patients who received RO7123520 reporting serious study drug-related adverse events of a similar nature (e.g., laboratory abnormalities, vital sign changes, ECG changes, etc.) *and* if there are no other reasons to stop the study (see Section 4.7.2).

All patients in Part 2 will have the option of continuing to the Extension Period of the study (Section 3.1.1.4).

3.1.1.3 Part 3: Phase IIb Dose-Ranging Study

Based on the results of an interim analysis planned during Part 2 of the study (Section 6.9), the Phase IIb dose-ranging part of the study will begin. Applying the same criteria as in Part 2 (i.e., patients with moderately to severely active RA experiencing an inadequate response to DMARD baseline therapy with MTX plus anti-TNF- α therapy), 105 patients will be randomized 2:2:2:1 to one of three selected RO7123520 doses, and placebo (or 5:5:5:1 if four RO7123520 doses and placebo are selected) in the range of 90 mg/dose to 720 mg/dose (e.g., 90, 180, 450 mg/dose). Final doses and the number of dose arms (3 or 4) for Part 3, along with the clarification of the sample size (Section 6.1) will be decided after analysis of safety and efficacy in the Part 2 interim analysis (Section 6.9). Patients will receive study treatment on Days 1, 14, 28, and 56, followed by the primary endpoint assessment at Week 12.

All patients in Part 3 will also have the option of continuing to the Extension Period of the study (Section 3.1.1.4).

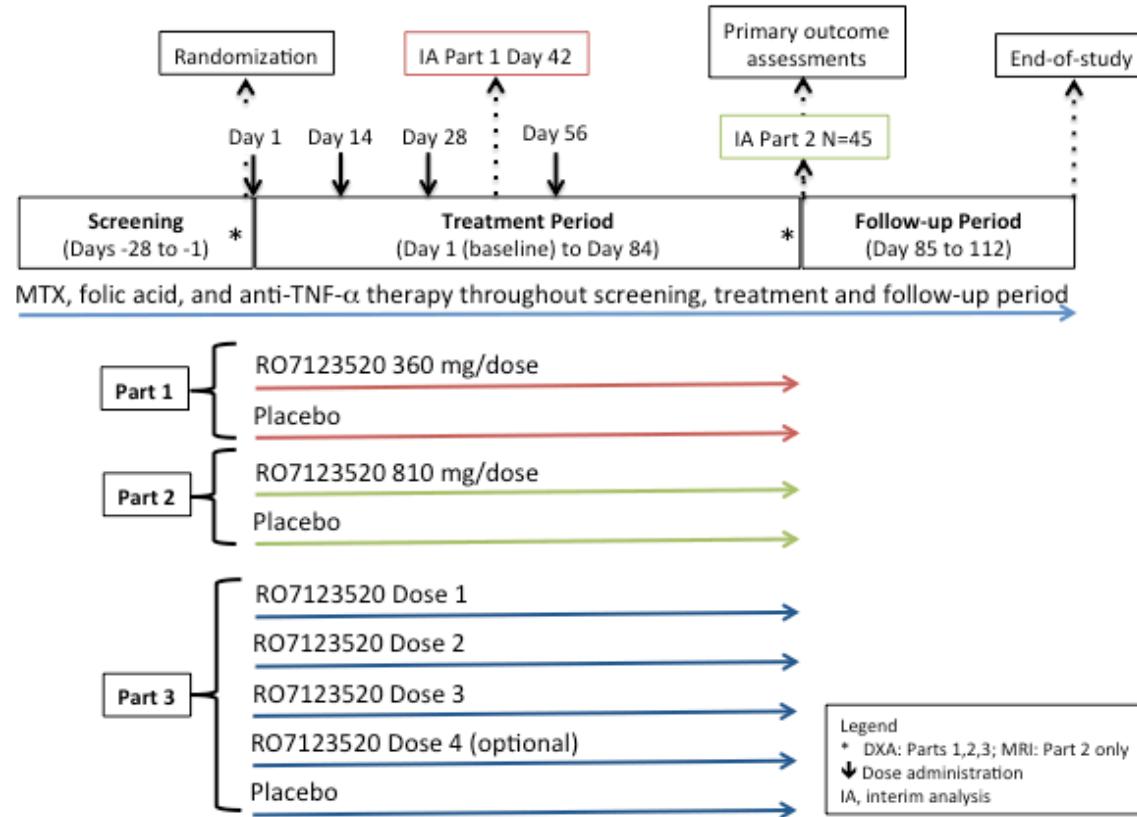
3.1.1.4 Extension Period

In Parts 1, 2 and 3, following the blinded, placebo-controlled 12-week study and Week 12 visit assessments, an optional extension period will be conducted to collect additional safety and efficacy data up to Week 24, with the last dose being administered at Week 20 (Appendix 2). A final safety visit will occur at Week 28 (German sites: Week 36).

Patients who received active treatments in Study Parts 1, 2 or 3 will continue on the same dose of RO7123520 as they previously received in Parts 1, 2 or 3. It is planned that patients who received placebo treatment in Part 1 will receive a 360 mg dose, while patients on placebo in Parts 2 or 3 will receive an 810 mg dose of RO7123520, although a lower dose may be employed at the recommendation of the IMC/SOC.

Figure 1 Study Design

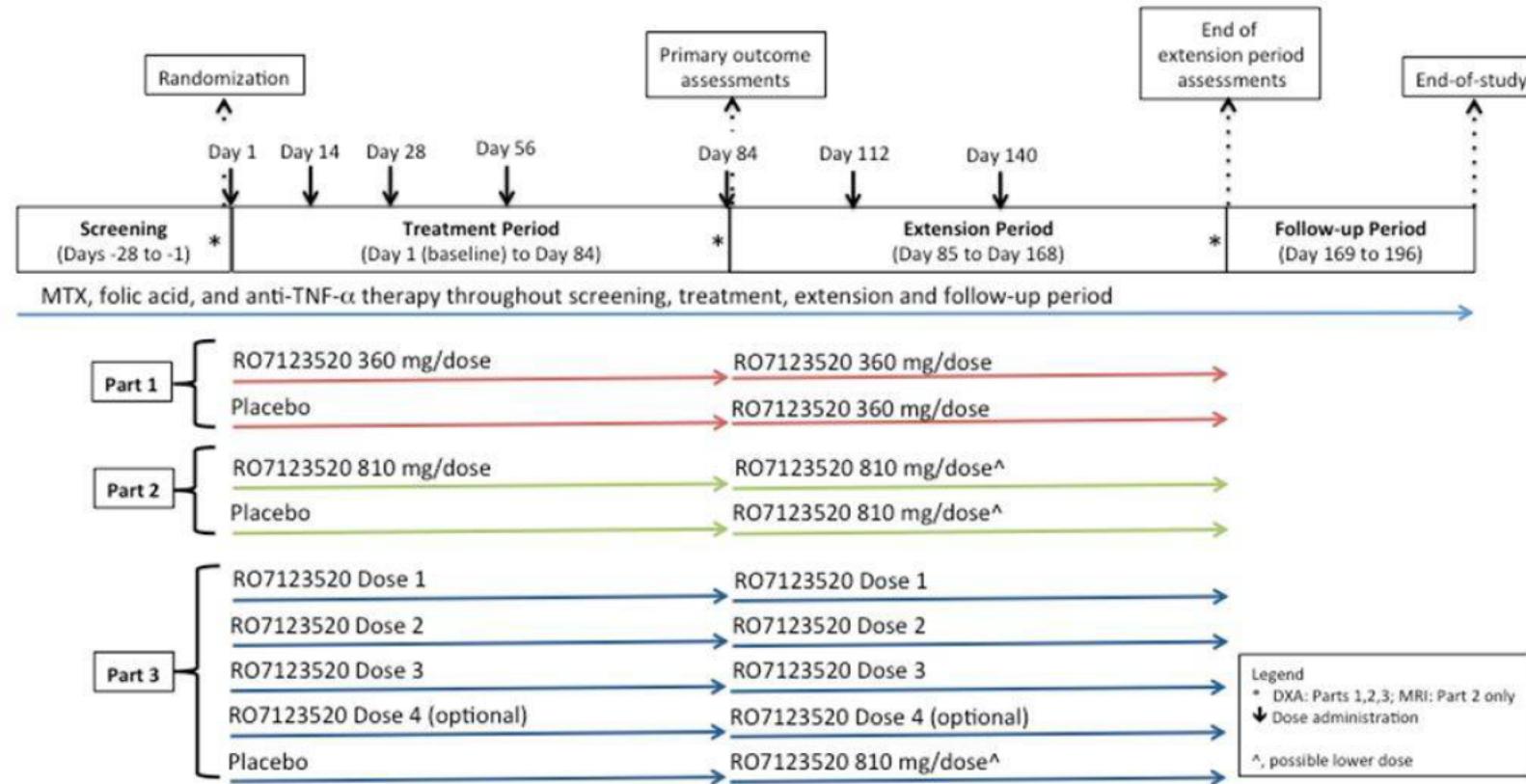
A. Parts 1, 2, and 3 without Extension Period



Note: This figure displays the follow-up period for non-German sites; for German sites, the follow-up period is from Day 85 to Day 168.

Figure 1 Study Design (cont.)

B. Parts 1, 2 and 3 with Extension Period



Note: This figure displays the follow-up period for non-German sites; for German sites, the follow-up period is from Day 169 to Day 252.

3.1.1.5 Study Duration

The total duration of the study for each patient will be up to 32 weeks (German sites: 40 weeks) divided as follows:

- Screening: Up to 4 weeks
- Study treatment duration: Days 1 up to 84 (Baseline to Week 12)
- Study treatment duration including Extension Period: Days 1 up to 168 (Baseline to Week 24)
- Safety Follow-up: Day 112 (Week 16). German sites: Day 112 (Week 16) and Day 168 (Week 24)
- Safety Follow-up including Extension Period: Day 196 (Week 28). German sites: Day 196 (Week 28) and Day 252 (Week 36)

Patients in Study Part 1 will be required to stay overnight at the Study Center after each dose of study treatment up to and including the Week 8 administration. The first 15 patients in Part 2 will be required to stay overnight at the Study Center after the first dose of study treatment, or alternatively, two visits within 24 hours post-dose can be made by an ambulatory at-home visiting nurse to perform assessments as described in the SoA.

3.1.2 Internal Monitoring Committee and Scientific Oversight Committee

To carefully review the accumulating safety data for RO7123520, and to decide upon the doses selected for inclusion into Part 3 of the study, an Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC) will be established.

The IMC will include Sponsor representatives from Translational Medicine, Drug Safety, Clinical Pharmacology and Biostatistics. The SOC members will be external experts in the field of RA. The SOC will function as a consultative body to the Sponsor, providing individual expert opinions. The Sponsor retains all decision-making authority for this study.

The first safety review meeting will be held once the 9th patient from Part 1 has completed the Week 6 visit (i.e., two weeks after their 3rd dose of RO7123520/placebo). The IMC and SOC will then meet approximately every month until the Part 2 interim analysis (Section 6.9) to review unblinded summaries of overall rates of death, SAEs, all AEs, and AEs leading to treatment discontinuation. In addition, the IMC and SOC will meet once the first 15 patients in Study Part 2 have completed their overnight stay after their first infusion of RO7123520/placebo, to determine whether the overnight stay will be a requirement for subsequent patients entering into Part 2 of the study. After the Part 2 Interim Analysis, the IMC and SOC will meet approximately every 3-6 months. All enrolled patients will be included in the safety summaries.

At the time of each review, the IMC and SOC will make one of the following recommendations: the trial continues as planned, a study arm stops, the protocol be amended, additional analyses be performed, or enrollment be held pending further safety evaluations. At the time of the interim analysis within Part 2 (Section 6.9), the IMC and SOC can also recommend the study stop for futility, or select the doses to be used in Part 3 and select the sample size for Part 3.

To maintain adequate patient safety oversight throughout the conduct of the study, all SAEs will be reviewed by the IMC Chair or delegate within 24–48 hours after being reported, and serious, unexpected, related AEs will be reviewed for regulatory reporting purposes per Roche standard operating procedures and will be submitted to the appropriate regulatory agencies, Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs), and to the Investigators.

Further interim exploration of safety may be performed, if deemed necessary, at any time during the conduct of the study.

3.1.3 End of Study

The end of the study is defined as the date when the last patient last observation (LPLO) occurs. LPLO is expected to occur 28 weeks (German sites: 36 weeks) after the last patient is enrolled.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Design

The study comprises three double-blind parts which will be run sequentially: Part 1 is an initial safety cohort intended to establish the safety and tolerability of repeat dosing of RO7123520 in patients with RA receiving MTX and anti-TNF- α therapy; Part 2 is intended to demonstrate the effectiveness of RO7123520 as a treatment for RA; while Part 3 is intended to characterize the dose vs. response relationship to identify the dose of RO7123520 with the optimal benefit-risk profile. The three part structure has been implemented to allow assessment of the safety and efficacy of RO7123520 in a staggered manner which minimizes the number of individuals exposed to study drug at each step. In particular, Part 1 is an initial safety cohort in a small number of patients (6 active, 3 placebo) to generate pharmacokinetic, safety and tolerability data before commencing with dosing in a larger number of patients in Part 2.

While Study SDP051-001 provided clinical experience of administration of single doses to healthy volunteers, this study represents the first study to test repeat dosing of RO7123520 in patients with RA also receiving MTX and anti-TNF- α therapy. Therefore, Part 1 includes design elements intended to minimize the potential risk to individual participants. These include use of a low dose of study drug (see Section 3.2.2), use of staggered dosing, a period of in-clinic residency and close medical supervision after each dosing, extensive safety monitoring measures, ongoing generation and review of

pharmacokinetic data, and periodic review of unblinded data by an IMC/SOC including members independent of the Sponsor.

Part 2 will only proceed if pre-specified safety criteria are met, and the IMC/SOC confirm that the study design remain appropriate (e.g., observed pharmacokinetic exposure data support original dose selection). Furthermore, Part 2 also includes a period of in-clinic residency and close medical supervision for first dosing for the first 15 patients enrolled, as well as review of unblinded data by an IMC/SOC. In this regard, the procedures for Parts 1 and 2 encompass all of the design elements typically expected in the early clinical development program for a new pharmaceutical agent with a novel mechanism of action.

The study also includes the possibility for patients who complete double-blind treatment to participate in an optional 12 week extension period in which all participants will receive RO7123520 treatment. This extension period is included to allow generation of data on longer-term use of RO7123520, and thereby help to characterize the benefit-risk profile from longer periods of treatment.

3.2.2 Rationale for Dosage Selection

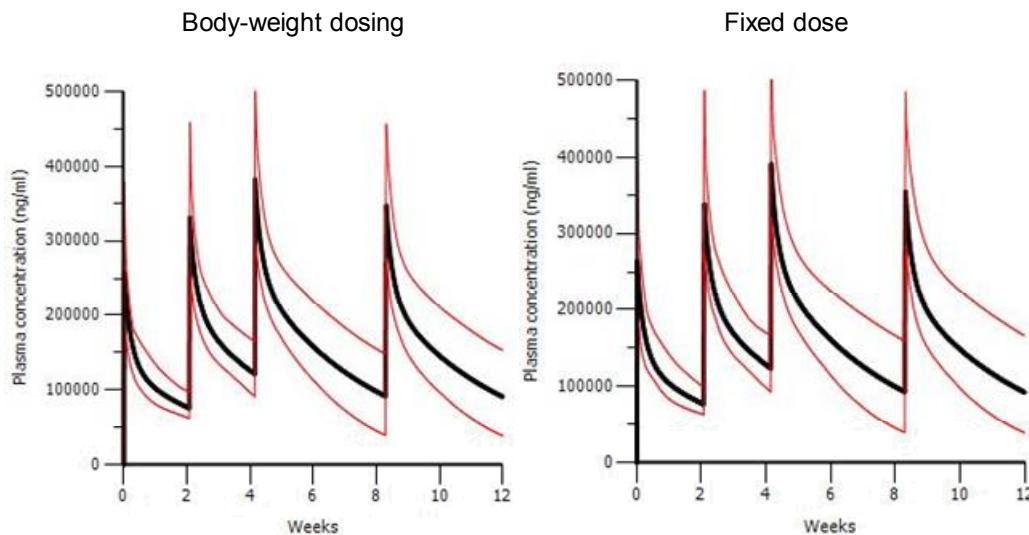
Selection of the proposed dosing algorithm, dosing regimen and range of doses to be investigated has been based primarily on modelling of pharmacokinetic data from the Phase I study SDP051-001 and simulations to predict RO7123520 exposures from multiple dosing under a variety of different dosing scenarios. Direct extrapolation of pharmacokinetic data from healthy volunteers to a patient population is possible based on the linear pharmacokinetic behavior of RO7123520 in Study SDP051-001 and the apparent absence of saturable pharmacokinetic processes (such as Fc receptor involvement in clearance) in the relevant concentration range. The available clinical safety and non-clinical pharmacology and toxicology data have also been used to inform the selection. Overall, doses have been selected which are predicted to produce exposures similar to those already studied in humans, and which also maintain margins versus NOAEL exposures in preclinical toxicology studies (see also Section 1.3.2).

3.2.2.1 Dosing Algorithm Selection

The pharmacokinetic model of data from Study SDP051-001 was used to explore the influence of intrinsic factors on RO7123520 pharmacokinetics and specifically to evaluate the need for a dosing algorithm incorporating body weight (i.e., mg/kg dosing). There was no apparent relationship between body weight and any of the four pharmacokinetic model parameters (V, CL, V2, or CL2). Similarly there was also no clear relationship between body weight and primary (V and CL) or secondary (AUC_{inf}, C_{max}, t_{1/2}) pharmacokinetic parameters estimated by non-compartmental methods. Hence, it is concluded that based on the available data from dosing in healthy volunteers, total body weight is not a good predictor of RO7123520 exposure. This is supported by simulations comparing the performance of body weight-adjusted dosing against a uniform “flat” dose (i.e., mg/kg dosing vs. same dose for all individuals regardless of

body weight). There were no apparent differences in average exposures, or corresponding ranges of exposures, between the two different algorithms (Figure 2). Therefore, a dosing algorithm based on individual body weight is not anticipated to reduce inter-individual variability in exposure compared with a uniform fixed dose.

Figure 2 Simulated Plasma Concentration versus Time Profiles from 10 mg/kg and 800 mg Dosing Algorithms

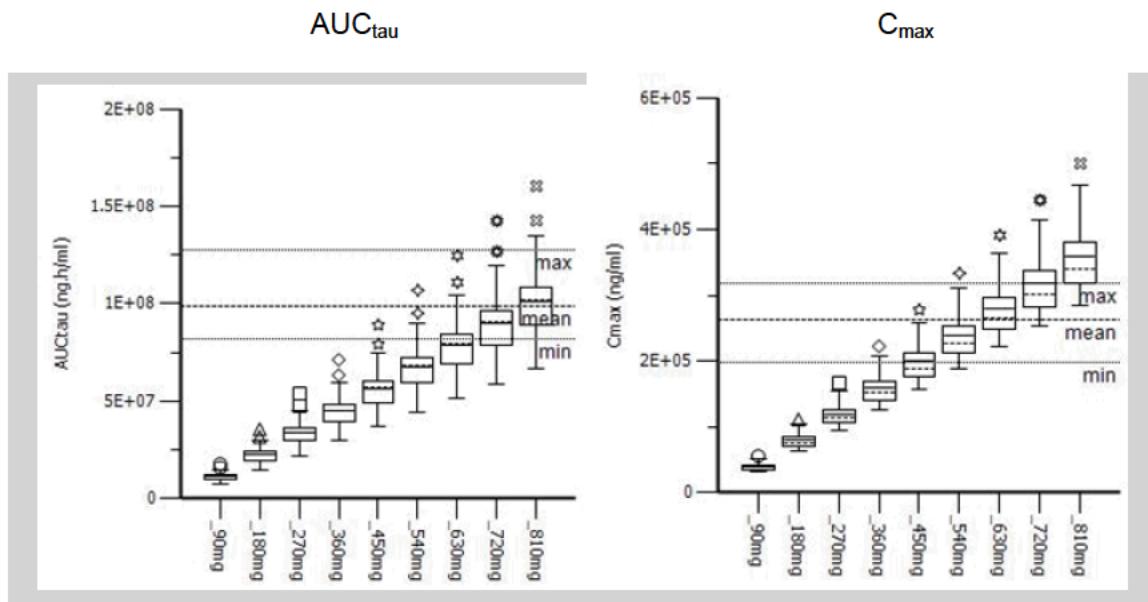


Black lines represent arithmetic mean, red lines represent associated 95% CIs.

3.2.2.2 Dosing Regimen Selection

To inform selection of an appropriate dosing regimen and dose, the same pharmacokinetic model was used to simulate RO7123520 plasma concentrations from a variety of different dosing schemes. These simulations predict that the proposed dosing regimen will lead to achievement of steady state after the second dose (i.e., Day 14 dose) (Figure 2) and no further significant accumulation in either the central or peripheral compartments is predicted even with continued monthly dosing. Simulations have been used to predict steady state RO7123520 exposures for different doses using the proposed dosing regimen (Figure 3).

Figure 3 Simulations of Predicted Steady-State RO7123520 Exposures for Different Doses using the Proposed Dosing Regimen



Solid horizontal box lines represent 25th, 50th (median) and 75th percentiles, dashed line represents arithmetic mean, “whiskers” indicate 1.5 × interquartile range, outliers beyond 1.5 × inter-quartile range shown as individual points.

Dashed and dotted horizontal lines indicate, maximum, mean and minimum observed exposures from 10 mg/kg dosing in Study SDP051-001.

3.2.2.3 Dose-Selection

The initial dose proposed to be tested in Part 1 is 360 mg/dose. Comparisons of predicted steady-state exposures from 360 mg dosing with corresponding observed exposures from single 10 mg/kg dose in Study SDP051-001 (Figure 3) indicate that exposures from 360 mg dosing should remain well within the range already demonstrated to be acceptably tolerated in healthy volunteers.

The highest dose proposed to be tested is 810 mg/dose. Comparisons of predicted steady-state exposures from 810 mg dosing (Figure 3) with observed exposures from single 10 mg/kg dose in Study SDP051-001 indicate that, although peak exposure immediately after dosing will be approximately 1/3 higher (steady-state C_{\max} 3.50×10^5 ng/mL vs. single dose C_{\max} 2.63×10^5 ng/mL), total exposure will be similar (steady-state AUC_{tau} 9.82×10^7 ng · h/mL vs. single dose AUC_{inf} 9.29×10^7 ng · h/mL). Furthermore, based on recent published information that average body weight of a population of patients with rheumatoid arthritis who have inadequate response to methotrexate and an anti-TNF- α therapy was 78 kg (Charles-Schoeman et al 2016) and hence, a RO7123520 dose of 810 mg should approximate to 10 mg/kg for a typical patient. Therefore, it is anticipated that exposures from 810 mg dosing will not

significantly exceed the range of exposures already demonstrated to be well tolerated in healthy volunteers.

Doses between 90 mg/dose and 810 mg/dose are anticipated to encompass a clinically-effective dose-range. Quantitative predictions of a clinically-effective dose-range have been based on in vivo studies in a relevant murine model of rheumatoid arthritis involving synovitis (the KBN model). RO7123520 reduced swelling of joints and joint destruction in a dose-dependent manner. At 10 mg/kg, RO7123520 significantly reduced joint inflammation, with a trend towards reduced joint swelling also at 3 mg/kg (see [RO7123520 Investigator's Brochure](#)). The reduction of joint swelling by RO7123520 was correlated with a reduction in joint destruction (e.g., reduced cartilage erosion, bone erosion and decreased inflammatory cell infiltrates) and a reduction in the levels of some cytokines implicated in rheumatoid arthritis pathogenesis in humans.

Although there has been no formal exposure versus response analysis, the observed serum concentrations of RO7123520 at doses which produce efficacy in the KBN model permits estimation of a potentially clinically efficacious exposure range in humans. A 10 mg/kg dose of RO7123520 produced average circulating concentrations of 125 µg/mL. Based on the observation that RO7123520 demonstrates similar binding to human and mouse Cad-11-expressing cells, and assuming that the relative distribution of RO7123520 into synovial joints is consistent between animals with KBN-induced arthritis and human patients with rheumatoid arthritis, it is considered that a serum concentration of approximately 100 µg/mL is a relevant exposure target to maximize the potential for detecting a treatment effect on efficacy parameters.

Using the pharmacokinetic model described above to simulate exposures from different doses ([Figure 2](#) and [Figure 3](#)), it is predicted that 810 mg/dose will provide serum exposures which achieve this target in most individuals e.g., average serum concentrations exceed 100 µg/mL throughout the dosing interval. For this reason, 810 mg/dose has been selected as the dose for Part 2. However, this prediction does not preclude the possibility that clinically-relevant treatment effects may be achieved from lower exposures, and therefore the dose-range-finding in Part 3 will also explore a range of lower doses in order to characterize the clinical exposure versus response relationship and establish the minimally effective dose. The lowest dose planned to be tested is 90 mg/dose, meaning that that overall a 9-fold range of doses will be tested.

3.2.3 Rationale for Study Population

Although there are a number of efficacious standard-of-care treatments (i.e., cDMARDs and biologics) for RA patients, many patients still experience significant ongoing disease activity. For example, a meta-analysis of different cDMARD and anti-TNF- α studies revealed that only 22%–58% (mean 39%) of RA patients achieve an ACR50 improvement, indicating that there are many patients who continue to have active disease ([Bergmann et al 2010](#)). Synovial fibroblasts are the major non-immune cell population of the inflamed RA joint and are thought to play a significant role in cartilage

destruction and in tissue inflammation. Therefore, targeting synovial fibroblasts comprises an attractive and novel non-immunosuppressive approach for interrupting pathophysiology of the RA joint, particularly if combined with existing DMARDs and biologics as an adjunctive approach to increase efficacy without increasing immunosuppressive side effects. Therefore, evaluating the efficacy and safety of RO7123520 as an adjunctive treatment in patients who have an inadequate response to the immunosuppressive therapy using MTX plus an anti-TNF- α therapy is reasonable.

Patients with RA will also potentially be taking a number of concomitant medications. These will include the protocol-specified anti-arthritis background therapy of the non-biologic DMARD, MTX, and biologic anti-TNF- α therapies (e.g., etanercept, adalimumab, certolizumab pegol, golimumab, etc.) but also miscellaneous other therapies for co-morbid conditions. There are no data available on the use of RO7123520 with MTX or biologic anti-TNF- α therapies, but clinically important drug-drug interactions are not anticipated for the following reasons:

- There is limited potential for pharmacokinetic drug-drug interactions between monoclonal antibodies and other therapies ([Ferri et al 2016](#)). Although it has been reported that MTX treatment reduces the clearance of some antibody based therapies used in RA (e.g., infliximab and adalimumab), this is hypothesized to arise from changes in target mediated drug distribution as a consequence of methotrexate-mediated reductions in TNF- α levels ([Xu et al 2015](#), [Ternant et al 2015](#)). This mechanism is considered not relevant for RO7123520.
- Based on the mode of action of RO7123520 (i.e., targeting the extracellular domain of the Cad-11 cell adhesion molecule), clinically important pharmacokinetic drug-drug interactions are not anticipated. In particular, RO7123520 has a novel mode of action that is distinct from those of MTX and anti-TNF- α therapies and other therapies currently in use for management of rheumatoid arthritis. Although it is reported that the COX2 selective non-steroidal anti-inflammatory drug celecoxib also inhibits Cad-11 ([Assefina et al 2014](#)), no other currently approved medications have the same mode of action. Therefore there is limited likelihood of direct pharmacodynamic interactions between RO7123520 and other medications.
- There is believed to be limited risk of interactions leading to clinically important safety concerns with other biologic therapies. RO7123520 does not appear to have direct effects on the immune system and PD effects are anticipated to be localized to those tissues where Cad-11 is expressed (i.e., predominantly the synovial joints). In the absence of systemic immunosuppressive effects from RO7123520, there is believed to be limited risk of clinically important immunosuppression from RO7123520 treatment, even when used in conjunction with immunosuppressive biologic therapies.

3.2.4 Rationale for Control Group

A placebo control group in Parts 1, 2, and 3 is justified in this early phase of development, as it will minimize the potential bias in reporting of adverse events, the

assessment of outcome measurements and assessment of laboratory abnormalities during the course of this study. Patients in the control group will be on placebo for 12 weeks, which is acceptable according to the EMA and FDA guidance for clinical trials in RA. Outcome measures in RA trials involve elements of subjective measures (e.g., patient's assessment of diseases status, pain, global function in ACR criteria) and therefore carry a high rate of placebo response (e.g., up to 11% non-specific ACR50 response) ([Azaïs et al 2016](#)). Therefore, the use of a placebo group in this randomized, double-blind, placebo-controlled trial is the most rigorous test for evaluating treatment efficacy of RO7123520.

3.2.5 Rationale for Biomarker Assessments

The biomarker strategy applied in this study aims to measure molecular markers that may be useful to define the prognosis and disease severity of the patients, to assess the mode of action/PD effects and to potentially identify predictive biomarkers. Specific blood cell markers will also be used as safety biomarkers.

All patients will be contributing mandatory serum, plasma and urine samples for biomarker measurements. Biomarkers may also be measured in synovial fluid and synovial tissue in patients who consent to fluid sampling (optional) and/or tissue biopsies (optional).

The potentially prognostic and disease severity markers measured will help to better characterize the patients in this study and will include the multi-biomarker disease activity (MBDA) test and type II collagen C-telopeptide (CTX-II). The MBDA test has been developed to analyze 12 protein biomarkers in serum, including interleukin-6 (IL-6) and C-reactive protein (CRP) ([Centola et al 2013](#)) and was identified as a good predictor for one year radiographic progression in early RA ([Hambardzumyan et al 2015](#)). Patients with high urinary CTX-II levels were found as having a higher risk for the progression of joint damage over one year ([Qvist et al 2011](#)).

The safety blood biomarkers, which will include T cells, B cells, NK cells, granulocyte and monocyte markers, will be monitored during treatment to confirm the non-immunosuppressive profile of RO7123520.

The selected PD biomarkers are expected to reflect the changes upon treatment in the various tissues and cellular components involved in the damaged joint affected by the disease, complementing the traditional efficacy endpoints (e.g., disease activity score 28 [DAS28], clinical disease activity index [CDAI], etc.) and imaging techniques used in the study. In particular, the bone remodeling and cartilage markers may include but will not be limited to C-terminal telopeptide of type I collagen (CTX-I), aminoterminal propeptide of type I collagen (PINP) and osteocalcin. Inflammatory, synovial and angiogenesis markers may also be measured, which are expected to be regulated upon Cad-11 engagement. The exploratory analysis of those markers should allow better understanding of the mode of action of RO7123520.

In addition, the potential utility of synovial fluid and synovial protein, and RNA biomarkers may be investigated to facilitate the understanding of the target and mode of action of RO7123520. The RNA biomarkers may be measured with next-generation sequencing (NGS) methods.

Cadherin-11 expression in synovium and synovial fluid might differ from patient to patient which might impact the response to the treatment. The expression of Cad-11 in the synovium *might* be measured by tissue staining while the soluble form of Cad-11 will be measured (shed Cad-11) in the synovial fluid of patients who consented to the sampling. *Blood soluble Cad-11 concentrations which might vary upon treatment may be measured by immunoassay.*

MRI scans will be performed to assess disease severity for patients in Study Part 2. Inflammatory lesions in the joints and the bone erosion will be evaluated, and soft tissue and bone marrow involvement will be assessed. The readings will be done centrally, by a blinded reader.

As active synovitis of the hand/wrist as determined by MRI is an inclusion criterion for active disease in Part 2 (Section 4.2.2), the central reader will also give the confirmation that this criterion is met.

3.2.6 Rationale for Pharmacokinetic Assessments

Samples will be collected at each visit for measurement of serum concentrations of RO7123520. These data will be used for population PK and PK/PD modelling at the end of Parts 2 and 3 of the study, but samples will be analyzed on an on-going basis and concentration data will also be reviewed as part of the periodic IMC/SOC reviews to verify that RO7123520 exposures are within the expected ranges.

RO7123520 concentrations will also be measured in synovial fluid samples collected at the end of treatment. These data will provide information on tissue distribution and drug exposures at the site of action. In addition, because the bioanalytical assay only detects free RO7123520 molecules that are not bound to Cad-11, synovial concentrations also have the potential serve as a surrogate marker of target engagement (i.e., detectable synovial RO7123520 concentrations implies a surplus of drug and complete target engagement).

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of adverse events, including targeted adverse events, number of participants with SAEs, treatment-related SAEs, SAEs leading to discontinuation, treatment-related AEs, or AEs leading to discontinuation

- Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- ECGs
- Vital signs
- Assessment of bone remodeling and cartilage markers (e.g., CTX-I, PINP and osteocalcin)
- Assessment of blood cell markers (including, but not limited to, CD4, CD8, CD19, CD16/56, CD3, CD45, CD14)
- Anti-drug antibodies (ADA)
- Bone mineral density lumbar spine L1-L4 by dual energy X-ray absorptiometry (DEXA) scans, which involves the exposure of a very small amount of X-ray radiation around one to six microSievert (μ Sv).

3.3.2 Pharmacokinetic Outcome Measures

RO7123520 serum and synovial fluid concentration data will be pooled with corresponding data from other studies (e.g., SDP051-001) for population PK and PK/PD modelling of the exposure versus response relationship.

3.3.3 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

Primary Outcome Measure:

- Proportion of patients achieving an ACR50 response at Week 12

Secondary Outcome Measures:

- Change from baseline in CDAI Score at Week 12
- Change from baseline in DAS28 at Week 12
- Proportion of patients achieving DAS28 remission at Week 12
- Proportion of patients achieving CDAI remission at Week 12
- Proportion of patients achieving an ACR20 response at Week 12
- Proportion of patients achieving an ACR70 response at Week 12
- Simple Disease Activity Index (SDAI) Score at Week 12
- Change from baseline in the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures for this study include but are not limited to the following:

- Proportion of patients achieving an ACR50 response at Week 24
- CDAI Score at Week 24
- DAS28 at Week 24
- Proportion of patients achieving DAS28 remission at Week 24
- Proportion of patients achieving CDAI remission at Week 24
- Proportion of patients achieving an ACR20 response at Week 24
- Proportion of patients achieving an ACR70 response at Week 24
- Proportion of patients achieving a mACR50 response at Weeks 12 and 24
- Proportion of patients achieving a mACR20 response at Weeks 12 and 24
- Proportion of patients achieving a mACR70 response at Weeks 12 and 24
- SDAI Score at Week 24
- Change from baseline in the Stanford HAQ-DI at Week 24
- Change from baseline in Short-form 36 health questionnaire Physical and Mental Health component scores (SF36V2 standard recall) at Weeks 12 and 24
- Change from baseline in Brief Fatigue Inventory (BFI) total and item scores at Weeks 12 and 24
- Change from baseline in patient global assessment of disease activity at Weeks 12 and 24
- Change from baseline in patient global assessment of pain at Weeks 12 and 24
- Change from baseline in Cad-11 synovium level in synovial fluid *and* blood soluble Cad-11 concentration at Weeks 12 and 24
- Change from baseline of the PD biomarkers (e.g., bone remodeling and cartilage markers) at Weeks 12 and 24
- Change from baseline in synovitis, osteitis, joint erosions, cartilage loss, bone marrow edema, total damage and total inflammation at Weeks 12 and 24 evaluated by rheumatoid arthritis MRI score (RAMRIS) of the hand/wrist

4. MATERIALS AND METHODS

4.1 CENTER

This is a multi-center study to be conducted in multiple countries. Additional site(s) may be included for back-up purposes and may be activated if needed.

Administrative and Contact Information, and List of Investigators are provided separately.

4.2 STUDY POPULATION

4.2.1 Recruitment Procedures

Patients will be identified for potential recruitment using pre-screening enrollment logs, IEC/IRB approved newspaper/radio/television/internet advertisements, social media, mailing lists, and referral letters to other physicians.

4.2.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Able and willing to provide written consent by signing the Informed Consent Form (ICF), and to comply with the study protocol according to ICH and local regulations.
2. Adult men and women, *of more than 18 years of age*.
3. Diagnosis of adult-onset RA as defined by the American College of Rheumatology (ACR) 2010 criteria ([Aletaha et al 2010](#)), for at least 6 months before screening.
4. Moderately to severely active RA as defined by at least 4/28 tender joints and at least 4/28 swollen joints (Note: surgically treated joints cannot be counted in TJC/SJC for enrollment purposes).
5. For Part 2 only: Active synovitis and/or osteitis as determined by contrast-enhanced MRI.
6. Patients must be taking one of the following anti-TNF- α therapies: certolizumab, golimumab, etanercept, adalimumab, *infliximab* or approved biosimilars of these, given at a *recommended* and stable dose for at least 12 weeks before randomization, and have experienced in the opinion of the Investigator an inadequate response to anti-TNF- α therapy with a DAS28 ≥ 3.2 .
Note: prior use of other anti-TNF- α therapies is allowed.

7. Patients must be taking MTX (PO, SC, or IM) for at least 12 weeks before randomization and must be on a stable dose for at least 4 weeks before randomization (5.0 to 25 mg/week).

Note: The dose of MTX is expected to remain stable throughout the study and may be adjusted only for safety or intolerance reasons. Local standard-of-care should be followed for concomitant administration of folic acid.

8. Patients on glucocorticoids (≤ 10 mg/day PO prednisone or equivalent) are permitted if doses are stable within 6 weeks of planned randomization.

Note: Patients should remain on stable doses of glucocorticoids throughout the duration of study unless for *medical reasons* (e.g., safety, intolerance, RA flare, etc).

9. Patients taking non-steroidal anti-inflammatory drugs (NSAIDs) intermittently (e.g., up to 2-3 times weekly) for short-term relief of pain are allowed, and patients on regular NSAID use (i.e., on stable dose for ≥ 4 weeks) are allowed.

Note: NSAIDs must not be taken for at least 2 days before clinical assessments in the study for patients with intermittent use of NSAIDs. If needed for symptomatic relief, paracetamol (up to 3 g/day) is permitted.

10. Negative pregnancy test at screening and baseline (women only), and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation as follows:

- Male or female patients: The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For males: men with female partners of childbearing potential or pregnant female partners must remain abstinent or use a condom during the treatment period and up to the post-treatment follow-up visit to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
- For females: Females are eligible to participate if not pregnant and not breastfeeding. A woman of childbearing potential and female partners with childbearing potential of male patients must agree to remain abstinent (refrain from heterosexual intercourse) or use one highly effective form of contraception that results in a failure rate of <1% per year during the treatment period and up to the post-treatment follow-up visit. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- Male and female patients should continue to use contraception after the last study drug administration until the end of relevant systemic exposure (i.e., ~115 days).

4.2.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Parenteral glucocorticoids administration (IM, IV) of ≥ 50 mg within 6 weeks or ≤ 50 mg within 4 weeks prior to planned randomization, or scheduled parenteral administrations during the study.
2. Joint(s) injected with intra-articular glucocorticoids within 6 weeks prior to planned randomization.
3. Active inflammatory diseases of the joints not related to RA: Gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease
4. Systemic autoimmune disease other than RA: Systemic lupus erythematosus, Crohn's disease, ulcerative colitis, systemic scleroderma, inflammatory myopathy, mixed forms of connective tissue inflammatory diseases.
5. Juvenile idiopathic arthritis or juvenile RA and/or RA developed before the age of 16.

6. Active fibromyalgia that makes appropriate assessment of RA disease activity challenging in the opinion of the Investigator.
7. RA patients functional status class IV according to the ACR 1991 criteria (i.e., largely or wholly incapacitated permitting little or no self-care, such as being bedridden or confined to wheelchair).
8. Patients with severe chronic or recurrent viral, bacterial, parasitic or fungal infections.
9. History of active hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection.
10. Any identified confirmed congenital or acquired immunodeficiency.
11. Abnormal laboratory values:
 - Hemoglobin level is less than 80 g/L.
 - Leucocyte level is less than 2.5×10^9 /L.
 - Absolute neutrophil count is less than 1.0×10^9 /L.
 - Thrombocyte level is less than 75×10^9 /L.
12. Laboratory test results for liver function meeting criteria for marked abnormality (ULN: upper limit of normal): Alkaline phosphatase: $> 3 \times$ ULN; aspartate aminotransferase: $> 3 \times$ ULN; alanine aminotransferase: $> 3 \times$ ULN; γ -glutamyl transferase: $> 3 \times$ ULN.
13. Other unstable somatic diseases apart from RA that can increase the probability of adverse events during the study; mask, enhance or alter the symptoms of RA or cause clinical or laboratory symptoms similar to that of RA.
14. Major surgery within 28 days prior to randomization, or *planned* major surgery (e.g., elective joint replacement surgery) during the trial.
15. Any mental disorder, including major depressive disorder and/or suicidal thoughts in anamnesis that can, in the Investigator's opinion, create a risk for the patient or influence the patient's ability to follow the study protocol.
16. Myocardial infarction within less than 6 months prior to participation in the study.
17. Severe central or peripheral nervous system diseases.
18. Chronic drug or alcohol abuse.
19. Known hypersensitivity to any components of the medications used in the study.
20. Acute forms of any infectious diseases or history of chronic infections with severe clinical manifestations that would increase risk in participation of trial in the opinion of the Investigator.
21. Presence of malignant neoplasm, with the exception of adequately treated basal cell carcinoma and cervical carcinoma in situ and any malignancy with complete remission of more than 5 years.
22. Simultaneous participation in any other clinical trial, as well as former participation in other clinical trials within 3 months before this study initiation; and previous study drug administration in this study.

23. German sites: Patients who are institutionalized due to regulatory or juridical order.
24. German sites: Patients who are occupationally or medically dependent on the Sponsor, the Investigator, or the medical site.

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally by an Interactive (voice/web) response system (IxRS) vendor. Patients will be stratified by the duration of prior anti-TNF- α therapy (3-12 months vs. > 12 months) for Study Parts 2 and 3.

The first 12 weeks of the study will be double-blind. Blinding to study treatment allocation will be achieved through administration of placebo (i.e., saline only) infusions. Neither the patient, nor the Investigator, nor the CRO and Sponsor personnel directly involved in managing the study, except for the members of the IMC/SOC, will be aware of the treatment allocation. The randomization list will, however, be made available to the staff at bioanalytical laboratories, and to the Sponsor personnel responsible for pharmacokinetic and pharmacodynamic bioanalysis, as well as members of the IMC/SOC. Access to data that are potentially unblinding (e.g., pharmacokinetic concentration data) will be restricted accordingly. The qualified individual responsible for dispensing the study drug will not be blinded.

Patients entering the Extension Period following 12 weeks in Study Part 1 will receive open-label RO7123520 360 mg throughout the Extension Period. Patients entering the Extension Period following 12 weeks in Study Part 2 will receive open-label RO7123520 810 mg throughout the Extension Period. Patients entering the Extension Period following 12 weeks in Study Part 3 will receive RO7123520 throughout the Extension Period and the RO7123520 dose level will be blinded to both the patient and Investigator (see Section 3.1.1.4 for details).

If unblinding is necessary for patient management (in the case of a serious adverse event), the Investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a SAE).

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAEs (see Section 5.1) that are considered by the Investigator to be related to study drug.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling

RO7123520 drug product (30 mg/mL) will be provided as a sterile, colorless to brown-yellowish liquid and contains no preservatives. Each single-use, 6 mL vial with a nominal 3.0 mL fill contains 90 mg (nominal) of RO7123520 formulated as 30 mg/mL in L-histidine/HCl buffer solution containing sodium chloride and polysorbate 20. For IV infusion, RO7123520 concentrate for solution for infusion should be diluted in 0.9% (w/v) sodium chloride solution prior to administration. The recommended storage conditions for the drug product are between 2°C-8°C and protected from light. The drug product must not be frozen.

Patients randomized to placebo will receive IV infusions of saline alone, therefore no actual matching placebo will be provided. It is not possible to differentiate between the IV bags which contain only saline and those which have RO7123520 added.

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

The study drug must be stored according to the details on the product label.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

For further details, see the [RO7123520 Investigator's Brochure](#) and the Pharmacy Manual.

4.4.2 Dosage, Administration and Compliance

Infusions will be administered IV over approximately 60 minutes or longer until the IV bag is empty. For further details on the preparation of RO70123520 for dosing, see the Pharmacy Manual. The administration of RO7123520 must be separated by at least one hour (end of administration first drug to start of administration second drug) from any other parenteral administration (anti-TNF- α , MTX or other).

Patients who receive active treatments in Study Parts 1, 2 or 3 and chose to participate in the optional extension period will continue on the same dose of RO7123520 they previously received in Parts 1, 2 or 3. Patients who receive placebo treatment in Part 1 and choose to participate in the optional extension will receive a 360 mg dose, while patients on placebo in Parts 2 or 3 will receive an 810 mg dose of RO7123520 although a lower dose may be employed at the recommendation of the IMC/SOC.

The qualified individual responsible for dispensing the study drug will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and patient number and initials on the study drug vial label and on the Drug Accountability Record. This individual will also record the study drug batch number received by each patient during the study.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section [5.1](#).

4.4.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (RO7123520) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, to confirm the shipment condition and content. Any damaged shipments will be replaced.

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study drug was dispensed (for example, patient initials and date of birth)
- All records and drug supplies must be available for inspection by the Roche Monitor [at every monitoring visit]

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, destroyed and provided that adequate storage and integrity of drug has been confirmed.

The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity [batch number] of investigational product[s] destroyed
- Quantity of investigational product[s] destroyed
- Date of destruction

- Method of destruction
- Name and signature of responsible person [or company] who destroyed investigational product[s]

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4.4 Post-Trial Access to RO7123520

The Sponsor does not intend to provide RO7123520 or other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.5 CONCOMITANT THERAPY

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements used by a patient from 30 days prior to screening until the follow-up visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All medications (prescription and over-the-counter [OTC]) taken within 30 days of study screening will be recorded on the appropriate eCRF.

All medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

Patients must be receiving stable regimens of MTX (i.e., 5.0 to 25 mg/week, per oral, subcutaneous, or intra-muscular application) and at least one anti-TNF- α therapy (from the following certolizumab, golimumab, etanercept, adalimumab, *infliximab* or approved biosimilars of these) in order to be eligible for the study. The *recommended* dose of anti-TNF- α therapy should be stable for at least 12 weeks, and the dose of MTX should be stable for at least 4 weeks before randomization. The doses should not be adjusted during the study except for safety or intolerance reasons.

Local standard-of-care should be followed for concomitant administration of folic acid.

Where possible all other concomitant medications (e.g., glucocorticoids, NSAIDs) should be kept stable during the study and only adjusted where clinically indicated, *e.g., as in RA flare*.

All prohibitions and requirements for treatment with anti-TNF- α therapies and MTX as described in local approved labelling are to be complied with by the Investigator and the patient.

4.5.1 Prohibited Therapy

The following medications are prohibited after randomization:

- Live vaccines, including herpes zoster vaccination. Non-live seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed.
- Any biologic therapy such as anti-IL-1, anti-IL-6, or T-cell or B-cell targeted therapies for any indication.
- Any interferon therapy for any indication.
- Any parenteral corticosteroid administered by IV injection.

4.5.2 Vaccination

Investigators should follow relevant local guidelines and standards of care for immunization of individuals with RA receiving MTX and anti-TNF- α therapy.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the schedule of assessments outlined in [Appendix 1](#) and [Appendix 2](#).

4.6.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, reproductive status, smoking history, use of alcohol and drugs of abuse. All medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within *30 days* prior to the screening visit will be recorded. The use of anti-TNF- α therapy in the last 12 weeks should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.6.1.2 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, and neurological systems *and should be done as indicated in Appendix 1*.

Any abnormality identified at baseline should be recorded on the appropriate eCRF.

Height (screening only) and weight will be recorded.

Additionally, or as clinically indicated, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.6.1.3 Skin Examination

A thorough skin examination will be conducted at every visit with detailed recording of findings. Patients will disrobe entirely and the entire skin, including the scalp, will be examined. Photographs may be taken for skin adverse events reported.

Detailed findings will be recorded in the eCRF.

4.6.1.4 Vital Signs

Blood pressure (BP), pulse rate, respiratory rate and body temperature will be recorded at the time-points specified in the Schedule of Assessments ([Appendix 1](#) and [Appendix 2](#)).

On days when study medication is administered, vital signs will be recorded pre-infusion, every 15 minutes during the infusion and at the end of the infusion.

Blood pressure, pulse rate and respiratory rate should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. All measurements will be obtained from the same arm and, with the same cuff size, using a well-calibrated automatic instrument with a digital readout, throughout the study (the "ideal" cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference [a length-to-width ratio of 2:1]). The automatic cuff should be placed on the designated arm at least 10 minutes prior to dosing. The patient should be asked to remove all clothing that covers the location of cuff placement. The individual should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). After the patient has been resting in supine position for at least 5 minutes, blood pressure, pulse rate and respiratory rate will be obtained.

4.6.1.5 Electrocardiograms

TriPLICATE ECG recordings (i.e., three useful ECGs without artifacts) will be obtained within approximately 2-5 minutes at each specified time-point. The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Whenever possible, the same brand/model of a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements should be used for each patient. The conditions should be as close as possible to pre-dose time-points; this includes but is not limited to food intake, activity level, stressors and room temperature.

To minimize variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to meals and

any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the patient's permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR will be calculated by the Sponsor/recorder on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

4.6.1.6 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at time-points specified in the Schedule of Assessments ([Appendix 1](#) and [Appendix 2](#)).

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for *an abnormal* urine or blood test, the test could be repeated.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the central laboratory. *Local laboratory analysis should only be used for study parameters related to AE/SAE. Erythrocyte sedimentation rate (ESR) may be performed locally.*

Samples for the following blood and urine laboratory tests will be collected and sent to the appropriate laboratory for analysis according to the lab manual:

- Hematology: leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
ESR, HsCRP

- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH
- Coagulation: international normalized ratio (INR), activated partial thromboplastin time (aPTT), prothrombin time (PT)
- Viral serology:
 - HIV (specific tests HIV-1 Antibody, HIV-1/2 Antibody, HIV-2 Antibody)
 - Hepatitis B surface antigen (HBsAg)
 - Total hepatitis B core antibody (HBcAb)
 - Hepatitis C virus (HCV) antibody
- Lipids: cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides
- Quantitative immunoglobulins: IgA, IgG, IgM, IgE
- Pregnancy test

All women of childbearing potential (including those who have had a tubal ligation) will have a blood pregnancy test at screening. Urine pregnancy tests will be performed at all subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

- Anti-drug antibodies
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, red blood cells [RBCs], white blood cells [WBCs], casts, crystals, epithelial cells, bacteria). Microscopy should only be performed when there are clinically significant positive or strong positive dipstick results.
- Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)

Based on continuous analysis of the data in this study, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

4.6.1.7 Additional Samples

The following samples will be collected for exploratory research:

- Whole blood for DNA and RNA analysis.
- Serum and plasma samples.

These samples will be destroyed no later than 15 years after the date of final clinical study report.

The residual material from PK, PD and exploratory biomarker samples will be destroyed within 3 years after the date of final clinical study report.

The synovial fluid and synovial tissue (collected from consenting patients from approved centers only) samples will be destroyed within 3 years after the date of final clinical study report. If the patient provides consent for optional exploratory research, the synovial tissue and fluid samples will be destroyed no later than 15 years after the date of final clinical study report or until no longer needed or used up.

For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

4.6.1.8 Immunogenicity Assessments

Blood samples for anti-drug antibodies (ADA) will be taken as described in the SoA ([Appendix 1](#) and [Appendix 2](#)). Samples collected from placebo treated patients will not be analyzed in the first instance, but retained for subsequent analysis if appropriate. ADA in serum will be determined using a validated enzyme-linked electrochemiluminescent assay (ECLA) method. Unused sample material may also be used for the purposes of concurrent assay improvement.

Details on sampling procedures, sample storage and shipment are given in the Sample Handling Manual.

4.6.1.9 PK Assessments

Blood samples for measurement of serum concentrations of RO7123520 will be collected at on-treatment visits as specified in the SoA ([Appendix 1](#) and [Appendix 2](#)). Samples will be collected at any convenient time before dosing, and one hour after the completion of the IV drug infusion. In addition, samples of synovial fluid collected will be used for measurement of synovial fluid concentrations of RO7123520.

RO7123520 serum and synovial fluid concentrations will be measured by a specific and validated enzyme-linked immunosorbent assay (ELISA) method. Samples collected from placebo treated patients will not be analyzed in the first instance, but retained for subsequent analysis if appropriate. Unused sample material may also be used for the purposes of concurrent assay improvement. Details on sampling procedures, sample storage, and shipment are given in the Sample Handling Manual.

4.6.1.10 Biomarker Assessments

Blood, Urine, Plasma and Serum Samples

Whole Blood, urine, plasma and serum samples will be collected for the following assessments:

- Multi-biomarker disease activity (MBDA) test
- Bone remodeling and cartilage markers (e.g., CTX-I, PINP and osteocalcin)
- Safety biomarkers which will include T cells, B cells, NK cells, granulocyte and monocyte markers.

Plasma/serum samples may also be used for analysis of inflammatory, synovial and angiogenesis markers.

Urine samples will be collected to measure CTX-II.

Synovial Fluid Samples

Synovial fluid aspiration, which will be done at two timepoints (or three in case of optional extension; see [Appendix 1](#) and [Appendix 2](#)), can be performed from the same joint being biopsied but should precede the biopsy. Samples will be processed for several protein biomarkers assessments and may be used for measuring RNA expression. The joint used for fluid aspiration is at the Investigator's discretion. If possible, the same joint should be aspirated during the study.

Synovial Biopsy Samples

Synovial biopsy samples will be taken by arthroscopy under local at two timepoints (or three in case of optional extension; [Appendix 1](#) and [Appendix 2](#)). Samples will be processed for routine histology, immunohistochemistry and potentially to assess RNA expression. The joint used for synovial biopsy is at the Investigator's discretion. If possible, the same joint should be assessed during the study.

Protein Biomarkers in Synovial Fluid

Protein biomarkers may include the following markers: MMP1, MMP3. Synovial fluid samples may also be used for analysis of inflammatory, synovial and angiogenesis markers.

Immunohistochemistry of Synovial Tissue

The immunohistochemical analyses may include the following markers: CD106, CD55. Analyses will include but not be limited to the above and involve further investigation in populations potentially involved in the etiopathogenesis of RA and related autoimmune conditions.

RNA Expression of Biomarkers in Synovial Tissue

RNA expression levels may be analyzed in synovial tissue by next generation sequencing (NGS) methods.

4.6.1.11 Disease-Specific Assessments

Swollen/Tender Joint Count (SJC/TJC)

An assessment of 66 joints for swelling and 68 joints for tenderness will be made. Joints will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis or fused joints will not be taken into consideration for swelling or tenderness. The joints to be assessed for swelling and tenderness are given in [Appendix 9](#).

Acute Phase Reactants

HsCRP will be analyzed centrally. Erythrocyte sedimentation rate (ESR) will be analyzed locally according to the standardized Westergren method.

MRI

For Part 2 only: Fat-suppressed, T1-weighted 3D gradient-echo and short tau inversion recovery (STIR) images of hand/wrist will be obtained with and without gadolinium contrast using 1.5T MRI and a hand frame to ensure reproducible positioning.

4.6.1.12 Patient-Reported Outcomes and Clinician-Reported Outcomes

Patient-reported outcomes (Patient Global Assessment of Disease Activity [PtGA], Patient Global Assessment of Pain [PtPA], HAQ-DI, Short Form Health Survey Version 2 [SF-36v2], and Brief Fatigue Inventory [BFI]) and clinician-reported outcomes (PGA) will be collected to help to characterize the clinical profile of RO712520.

The global assessment visual analogue scale (VAS) items (PtGA, PtPA and PGA) will be included in all composite assessments requiring these items (DAS28, CDAI and SDAI).

The instruments will be translated as required in the local language and completed in their entirety at specified time-points during the study. Patients will complete questionnaires using an electronic ePRO device, specific to each study visit day/week. To ensure instrument validity and that data standards meet Health Authority requirements, questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO and clinician-reported outcome assessments, and prior to the administration of study treatment, unless otherwise specified.

Patient Global Assessment of Disease Activity (PtGA)

The PtGA represents the patient's overall assessment of their current disease activity on a 100 mm horizontal visual analogue scale (VAS). The extreme left end of the line is described as no disease activity (symptom-free and no arthritis symptoms) and the

extreme right end as maximum disease activity (maximum arthritis disease activity) ([Appendix 3](#)). Visually-impaired patients unable to complete the VAS will be asked to give the score verbally.

Physician Global Assessment of Disease Activity (PGA)

The PGA represents the physician's assessment of the patient's current disease activity on a 100 mm horizontal VAS. The extreme left end of the line is described as no disease activity (symptom-free and no arthritis symptoms) and the extreme right end as maximum disease activity ([Appendix 4](#)).

Patient's Global Assessment of Pain (PtPA)

The PtPA represents the patient's assessment of his/her current level of pain on a 100 mm horizontal VAS. The extreme left end of the line is described as no pain and the extreme right end as most severe pain ([Appendix 5](#)).

Health Assessment Questionnaire (HAQ-DI)

The HAQ-DI will be used to assess patient's physical functioning. The HAQ-DI is a 20-item, validated questionnaire used to assess difficulty in performing activities of daily living ([Fries 1983](#)). The HAQ-DI refers to the previous week and assesses eight domains of physical functioning: Dressing and Grooming (2 items), Hygiene (3 items), Arising (2 items), Reach (2 items), Eating (3 items), Grip (3 items), Walking (2 items), Common Daily Activities (3 items). The questions assess usual abilities ranging from 0 "without any difficulty" to 3 "unable to do." A lower HAQ-DI score indicates better quality of life ([Appendix 6](#)).

Short-form Health Survey (SF-36v2)

The SF-36v2 will be used to assess health-related quality of life (HRQoL; [Ware and Sherbourne 1992](#)). The 36-item questionnaire consists of 8 domains: Physical Functioning (10 items), Role-Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role-Emotional (3 items), Mental Health (5 items), and an additional item on reported health transition. The SF-36v2 has a recall specification of 4 weeks and items are assessed on Yes/No and 5- to 6-point Likert scales. A higher score indicates better health ([Appendix 7](#)).

Brief Fatigue Inventory (BFI)

The BFI will be used to assess the level and impact of fatigue experienced by patients ([Mendoza et al 1999](#)). The BFI is comprised of 4 items: the first is a single-item not included in scoring. The second is a single-item assessing patient's usual level of fatigue, the third rates the patient's fatigue at its worst in the past 24 hours, and the final item is comprised of 4 questions which rate the interference from fatigue. Items 2, 3 and 4 comprise the total BFI score. All items are rated on an 11-point numeric rating scale (NRS-11), with 0 as "no fatigue/interference" and 10 "bad as you can imagine/complete interference." The BFI is appropriate for use in an RA population ([Wolfe et al 2004](#)) ([Appendix 8](#)).

Morning Stiffness

The patient's assessment of morning stiffness will be collected as duration (hours and minutes) of morning stiffness ([Appendix 10](#)).

4.6.1.13 Samples for Research Biosample Repository

Overview of the Research Biosample Repository

The Roche Research Biosample Repository (RBR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of these specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens will be collected from patients who give specific consent to participate in this optional Research Biosample Repository. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression.
- To increase knowledge and understanding of disease biology.
- To study drug response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Residual synovial tissue and fluid from any patient who consents to their collection and to store in RBR post-study
- Plasma and serum to assess for biomarkers
- Blood for DNA and RNA extraction to assess for biomarkers

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Blood for DNA extraction to assess for biomarkers

The samples collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis and may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

RBR specimens will be stored and used until no longer needed or until they are exhausted. The Research Biosample Repository storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality and in Section 8.4).

Confidentiality

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local Health Authorities, and Roche Monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RBR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RBR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Patients will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with investigators or patients unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR specimen data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The Investigator should document whether or not the patient has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a patient who is participating in the Research, the participant's specimens and data will continue to be used as part of the RBR.

Withdrawal from the Research Biosample Repository

Patients who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the patient's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the Research Biosample Repository Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BP39261 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BP39261. Data already generated before time of withdrawal of consent to Research Biosample Repository will still be used.

Monitoring and Oversight

Specimens collected for the Research Biosample Repository will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche Monitors and auditors will have direct access to appropriate parts of records relating to patient participation in Research Biosample Repository for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patient and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments will be performed within 28 days prior to Day 1, unless otherwise specified. Patients who fail screening may be able to re-screen once. In order to re-screen a patient, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments, including MRI scan, should be repeated if done more than 28 days before randomization. There is no need to repeat bone mineral density if it has been done for the study within 6 months before re-screening.

4.6.2.2 Assessments during Treatment

Under no circumstances will patients who enroll in this study and have completed treatment as specified, be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as per SoA (see [Appendix 1](#) and [Appendix 2](#)). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. The exact assessments may vary by specific visit date and the sequence will be standardized as follows (at visits as specified in the SOA):

1. Patients will complete health outcomes assessments using an electronic ePRO device, specific to each study visit day/week.
 - SF36v2
 - HAQ-DI
 - BFI
 - PtPA (pain VAS)
 - PtGA (Global Assessment of disease activity VAS)

2. Laboratory samples for safety, efficacy, PD and PK; must be drawn after patient self-assessments are completed, at least 30 min before Investigator assessments or at any time after nurse/Investigator assessments but prior to study drug infusion.
Note: providing all listed restrictions are met, the lab samples can be collected before or after the joint count is performed.
3. Investigator assessments:
 - Joint counts
 - Physician's global assessment of disease activity VAS, safety assessments (adverse events, vital signs, concomitant medications, review of laboratory data)
4. RO7123520/placebo infusion
5. Post-dose vital signs, post-dose PK (at the visits scheduled), adverse events.

4.6.2.3 Safety Follow-up Phone Call

Patients in Study Parts 1 and 2 will receive a safety follow-up telephone call two weeks after each dose of the study medication, at the timepoints shown in the SoA ([Appendix 1](#) and [Appendix 2](#)), if they are not otherwise visiting the Study Center.

4.6.2.4 Assessments at Study Completion/Early Termination Visit

Patients who complete the study or discontinue from the study early will be asked to return to the clinic 8 weeks (German sites: 8 and 16 weeks) after the last dose of study drug for a follow-up visit.

4.6.2.5 Follow-Up Assessments

After the study completion/early termination visit, adverse events should be followed as outlined in Sections [5.5](#) and [5.6](#).

4.6.2.6 Assessments at Unscheduled Visits

Assessments at unscheduled visits are based on the medical need of the patient.

Assessments that are conducted at regular scheduled visits can be conducted at unscheduled visits at the discretion of the Investigator.

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The Investigator has the right to discontinue a patient from RO7123520 or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

- Patient non-compliance: Patients who miss more than one scheduled dose or miss the Week 8 scheduled dose of study medication should be withdrawn from the study.

4.7.1.1 Discontinuation from Study Drug

Patients must discontinue study drug if they experience any of the following:

- Pregnancy
- Severe skin adverse reactions
- Severe hypersensitivity reactions
- Reduction in bone mineral density of clinical significance (e.g., significant loss of height over the course of the study, back pain suspected to be caused by fractured or collapsed vertebra, fragility)

Patients who discontinue study drug prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 4.6.2.4) and may undergo follow-up assessments (see Section 4.6.2.5). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.7.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Patients will not be followed for any reason after consent has been withdrawn.

When a patient voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless patient specifically requests for these to be discarded or local laws require their immediate destruction. A patient's withdrawal from Study BP39261 does not, by itself, constitute withdrawal of specimens donated to the Research Biosample Repository.

Patients who withdraw from the study for safety reasons will not be replaced. Patients who withdraw from the study for other reasons will not be replaced.

4.7.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

- Enrollment and study progression from Part 1 to Part 2 or from Part 2 to Part 3 will be put on hold pending full data review if more than 30% of patients on active study drug experience drug-related SAEs of similar nature (see Sections 3.1.1.1 and 3.1.1.2). The study will be stopped if the benefit-risk ratio changes to be unacceptable in this indication as judged by the Sponsor and the IMC/SOC.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.1.2.

5.1.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death).
- Life-threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death).

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.10](#)).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#) for reporting instructions).

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the

event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- Suspected transmission of an infectious agent by the study drug, as defined below:
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2 SAFETY PLAN

5.2.1 Management of Specific Adverse Events

For the adverse events listed below, standard-of-care should be provided at the Investigator's discretion. For more details please refer to the [RO7123520 Investigator's Brochure](#).

5.2.1.1 Contact Dermatitis

In the Phase I study SDP051-001, there were 6 cases of mild contact dermatitis plus one case of application site reaction, all in the active treatment groups. A thorough skin examination will be performed at every visit with detailed recording of findings. Photographs may be taken for skin adverse events reported. Dermatology consultation and biopsy will be taken on an ad hoc basis. Study drug will be discontinued in patients with skin adverse reactions that are considered Severe.

5.2.1.2 Headache

In the Phase I study SDP051-001, there were 4 cases of mild headache in the active treatment group and none in placebo. Adverse event reports will be monitored.

5.2.1.3 Hypersensitivity

Hypersensitivity is a theoretical risk for all biologic compounds. Adverse events will be monitored and treatment given according to standard of care. Study drug will be discontinued in patients with severe adverse reactions.

5.2.1.4 Reduced Bone Density

This is a theoretical risk for reduced bone mineral density as Cad-11 is expressed in osteoblasts. Bone density will be measured during this study. There are no inclusion or exclusion criteria regarding this event and no specific discontinuation criteria.

5.2.1.5 Impaired Wound Healing

There is a theoretical risk that inhibition of Cad-11 can impair fibroblast function and wound healing. Adverse events will be monitored, especially in patients who develop

wounds or have surgical procedures. There are no inclusion or exclusion criteria regarding recent surgery and no specific discontinuation criteria.

5.2.1.6 Decreased Fertility

Cad-11 is believed to play a role in trophoblast implantation. This is a theoretical risk in female patients. Female patients of childbearing potential are required to use highly effective birth control.

5.2.1.7 Teratogenicity

This is a theoretical risk based on the role of Cad-11 on mesenchymal tissue and organ development. Highly effective birth control is to be used by female patients, and male patients are to use condoms to avoid a vaginal dose.

5.2.1.8 Serious Infection

Infections are not expected with anti-Cad-11 but are known to be a risk for concomitant medications being used in this study. Adverse event reports will be closely monitored.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 to Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures, such as biopsies). Any other adverse event should not be reported.

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the follow-up visit after the last dose of study drug.

After the last dose of study drug and until the follow-up visit, Investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time-points. Examples of non-directive questions include the following:

“How have you felt since your last clinic visit?”

“Have you had any new or changed health problems since you were last here?”

5.3.3 Assessment of Severity of Adverse Events

[Table 1](#) provides guidance for assessing adverse event severity.

Table 1 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section [5.1.2](#)).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study drug, or reintroduction of study drug
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patient receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug RO7123520 infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction". Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

Other Adverse Events

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

Therefore, Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of RA.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the general medical history and baseline conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Lack of Efficacy or Worsening of Rheumatoid Arthritis

Medical occurrences or symptoms of deterioration that are anticipated as part of RA should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of RA on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated RA”).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The patient has not suffered an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.11 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies
- *Accidental overdoses or medication errors (see Section 5.4.4. for details on reporting requirements).*

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery

- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitor is available 24 hours a day 7 days a week. Medical Monitor contact details are listed in the “Protocol Administrative and Contact Information & List of Investigators”.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the SAE Responsible immediately (i.e., no more than 24 hours after learning of the event).

5.4.2.2 Events That Occur after Study Drug Initiation

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 5.1.2 and 5.1.3) that occur after initiation of study drug, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest /Serious Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor’s Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the SAE Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within **115 days** after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the investigator and submitted to the sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks

of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

5.4.3.2 Pregnancies in Female Partners of Male Patient

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 115 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the investigator and submitted to the sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Elective abortion not associated with toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- *Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose*
- *Medication error: accidental deviation in the administration of a drug*

In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with RO7123520, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- *Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.*
- *Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.*

For RO7123520, each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4). For RO7123520, adverse events associated with special situations should be recorded as described below for each situation:

- *Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section [5.4.3](#).

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 8 weeks [German sites: 16 weeks] after the last dose of study drug).

If the Investigator becomes aware of any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- RO7123520 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

Part 1:

No formal sample size estimation was performed for Part 1 of the study. A total of 9 patients (6 on the RO7123520 arm and 3 on the placebo arm) is deemed sufficient to provide initial safety information on RO7123520 in RA patients.

Part 2:

A total of 90 patients will be randomized 2:1 to either the RO7123520 or placebo arm. The probability of observing a difference of at least 15% between the RO7123520 and placebo Week 12 ACR50 response rates is approximately 0.73, assuming that the *true* ACR50 response rate on placebo is 15% and 35% on RO7123520. With 60 patients receiving RO7123520 810 mg, there is at least a 95% chance of observing an AE with true incidence of $\geq 5\%$. Ninety patients will therefore give a reasonable assessment of the safety and efficacy of RO7123520 before progressing to Part 3.

Part 3:

Following the decision to initiate Part 3 at the interim analysis of Part 2 of the study or after the end of Part 2 (when all 90 patients have reached the Week 12 visit) (Section 6.9), 105 patients will be randomized 2:2:2:1 to one of 3 selected RO7123520 doses, and placebo (or 5:5:5:5:1 if four RO7123520 doses and placebo are selected).

The total sample size for the combined Study Parts 1, 2 and 3 will be 204 patients (either 60, 30, 30, 30 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 48 receiving placebo, or 60, 25, 25, 25, 25 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 38 receiving placebo). This provides approximately 80% power of observing a positive dose response curve with a maximum effect of RO7123520 compared to placebo of -8.0 in change from baseline in CDAI score at Week 12 (placebo change from baseline in CDAI is assumed to be -10.0, with a common standard deviation of 15.0), allowing for a 10% drop-out rate and using a two-sided alpha level of 0.1.

If conflicting results are observed from Study Part 2 of the study between the change from baseline in CDAI at Week 12 endpoint and ACR50 response at Week 12 endpoint, then the following sample size for Part 3 will be undertaken and the dose-response analysis will be based on ACR50 at Week 12:

A total sample size of 150 patients will be recruited into Part 3 of the study. Therefore the total sample size for the combined Study Parts 1, 2 and 3 will be 249 patients (either 60, 45, 45, 45 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 48 receiving placebo, or 60, 36, 36, 36, 36 receiving different doses of RO7123520, plus 6 RO7123520 patients from Study Part 1, and 39 receiving placebo), which provides approximately 80% power of observing a positive dose response curve using a two-sided alpha level of 0.1, and assuming a placebo ACR50 response of 15% and active RO7123520 response of 35%, i.e., a delta effect size of 20%.

6.2 SUMMARIES OF CONDUCT OF STUDY

The numbers of patients, who enroll, discontinue, and complete the study, will be tabulated by treatment group. Reasons for premature study discontinuation will be listed and summarized by treatment group. Any major protocol deviations will be captured and listed.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All patients who have received at least one dose of the study medication, whether prematurely withdrawn from the study or not, will be included in the safety analysis population.

6.3.2 Efficacy Analysis Population

All randomized patients will be included in the efficacy analysis population.

6.3.3 Immunogenicity Analysis Population

The immunogenicity analyses will include patients with at least one predose ADA assessment, with patients grouped according to treatment received and dose level.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up visit will be summarized by treatment group and dose level.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and pretreatment characteristics such as age, sex, race, ethnicity, duration of RA, previous and background therapies for RA, weight, DAS28 score, CDAI score, CRP, ESR, joint counts, HAQ-DI score, physician's global assessment of disease activity, patient's global assessment of disease activity, and patient's assessment of pain will be summarized by treatment group and dose using the efficacy analysis population. The potentially prognostic and disease severity biomarkers MBDA and CTX-II (Section 3.2.5) will also be summarized by treatment group and dose using the efficacy analysis population.

Continuous data (e.g., age, body weight, and DAS28) will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum). For categorical data (e.g., race and sex), the number and percentage of participants in each category will be presented.

Baseline will be defined as the latest assessment prior to the first infusion of RO7123520/placebo.

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population and reported by the treatment group and dose actually received.

6.5.1 Adverse Events

The original terms recorded on the eCRF by the investigator for adverse events will be standardized by the sponsor.

Adverse events will be summarized by mapped term and appropriate thesaurus level.

Incidence, nature and severity of adverse events, including targeted adverse events, number of participants with serious adverse events (SAEs), treatment-related SAEs, SAEs leading to discontinuation, treatment-related AEs, or AEs leading to discontinuation will be tabulated by treatment group and dose.

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Patient listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International

d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.

6.5.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

6.5.2.2 Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in patient listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a patient, the midpoint of the standard reference range will be used as the patient's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the patient listings as "HH" for very high or "LL" for very low.

6.5.3 Vital Signs

Vital signs and weight data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.5.4 ECG Data Analysis

ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.5.5 Concomitant Medications

The original terms recorded on the patients' eCRFs by the investigator for concomitant medications will be standardized by the sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.6 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all patients in the efficacy analysis population, with patients grouped according to the treatment and dose assigned at randomization.

6.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint to demonstrate the proof of concept of RO7123520 is the proportion of patients achieving an ACR50 response at Week 12 using RO7123520 as adjunct therapy to MTX+anti-TNF- α compared to MTX+anti-TNF- α plus placebo.

An ACR50 response is defined by achieving an improvement of $\geq 50\%$ compared to baseline in the American College of Rheumatology (ACR) core set of outcome measures in both SJC and TJC as well as in 3 out of 5 additional parameters: physician's global assessment of disease activity (PGA, Section [4.6.1.12](#)), patient's global assessment of disease activity (PtGA, Section [4.6.1.12](#)), patient's assessment of pain (PtPA), HAQ-DI, and acute phase reactant (CRP will be used as the ACR APR in this study).

Patients who withdraw from the study prior to the Week 12 ACR assessment, and all patients in whom the Week 12 ACR50 response cannot be determined for any reason, will be considered non-responders for the summaries of ACR50.

The proportion of patients achieving an ACR50 response at Week 12 will be summarized descriptively by treatment/dose arm.

6.6.2 Secondary Efficacy Endpoints

Clinical Disease Activity Index (CDAI) Score

The CDAI is a composite endpoint score including swollen 28-joint count (SJC28), tender 28-joint count (TJC28), PtGA and PGA. CDAI score is calculated as follows:

$$CDAI = SJC28 + TJC28 + PtGA + PGA$$

The change from baseline in CDAI score at Week 12 will be included in the dose-response assessment at the end of Part 3 of the study. The dose-response relationship will be assessed using a MCP-mod approach ([Bretz et al 2005](#)), including the data from all three study parts. The candidate models will be fitted to the change from baseline in CDAI at Week 12 and multiple contrast tests (two-sided $\alpha=0.1$) will be produced along with the corresponding multiplicity adjusted p-values. From the statistically significant

candidate models, the most appropriate (based on Akaike information criterion [AIC]) will be selected and the target dose will be the dose which demonstrates a change from baseline in CDAI at Week 12 of -8.0 relative to the placebo change from baseline value. Full details will be included in the study statistical analysis plan (SAP).

If conflicts in the change from baseline in CDAI and ACR50 response results are observed at the time of the Part 2 interim analysis (Section 6.9), then the ACR50 response (Section 6.6.1) may be chosen as the endpoint for assessing the dose-response. The methodology will be the same as for the change from baseline in CDAI dose-response as described above. If ACR50 response is used for the dose-response endpoint then the target dose will be selected as the dose which demonstrates a 15% difference between the RO7123520 response rate and the placebo response rate.

The change from baseline in CDAI at Week 12 and the actual CDAI score at Week 12 will also be summarized descriptively by treatment/dose arm.

Missing CDAI scores will not be imputed.

ACR20, ACR70

Achievement of an ACR20 requires a $\geq 20\%$ improvement in the same parameters as ACR50 (see Section 6.6.1) and an ACR70 requires a $\geq 70\%$ improvement.

The proportion of patients achieving an ACR20 response at Week 12 and the proportion achieving an ACR70 response at Week 12 will be summarized in the same manner as for the ACR50 endpoint described in Section 6.6.1.

Patients who withdraw from the study prior to the Week 12 ACR assessment, and all patients in whom the Week 12 ACR20/ACR70 response cannot be determined for any reason, will be considered non-responders for the summaries of ACR20/ACR70.

Disease Activity Score (DAS28)

The DAS28 is a combined index for measuring disease activity in RA. The index includes swollen and tender joint counts, acute phase response (ESR will be used as the DAS28 APR in this study), and general arthritis disease activity status. The index is calculated using the following formula:

$$DAS28 = 0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times PtGA$$

Where, TJC28 = tender joint count on 28 joints, SJC28 = swollen joint count on 28 joints, \ln = natural log, ESR = Erythrocyte sedimentation rate (mm/hr), and PtGA (Section 4.6.1.12). The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.

The change from Baseline in DAS28 score at Week 12 will be summarized descriptively by treatment/dose arm.

Missing DAS28 scores will not be imputed.

DAS28 Remission

The proportion of patients achieving DAS28 remission at Week 12 will be summarized descriptively by treatment/dose arm.

DAS28 remission is defined as a DAS28 score <2.6.

Patients who withdraw from the study prior to the Week 12 visit, and all patients in whom the Week 12 DAS28 score cannot be determined for any reason, will be considered non-responders for the summaries of DAS28 remission.

CDAI Remission

The proportion of patients achieving CDAI remission at Week 12 will be summarized descriptively by treatment/dose arm.

CDAI remission is defined as a CDAI score ≤ 2.8 .

Patients who withdraw from the study prior to the Week 12 visit, and all patients in whom the Week 12 CDAI score cannot be determined for any reason, will be considered non-responders for the summaries of CDAI remission.

Simple Disease Activity Index (SDAI) Score

The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28 - joint assessment), PtGA (Section [4.6.1.12](#)), PGA (Section [4.6.1.12](#)) and level of CRP (mg/dl) as follows:

$$SDAI = SJC28 + TJC28 + PtGA + PGA + CRP$$

The change from Baseline in SDAI at Week 12 and also the actual SDAI score at Week 12 will be summarized descriptively by treatment/dose arm.

Missing SDAI scores will not be imputed.

Health Assessment Questionnaire (HAQ-DI)

The HAQ-DI is a self-completed questionnaire described in Section [4.6.1.12](#).

The change from Baseline in HAQ-DI at Week 12 will be summarized descriptively by treatment/dose arm.

Missing HAQ-DI scores will not be imputed.

6.7 PHARMACOKINETIC ANALYSES

RO7123520 concentration data will be pooled with data from other studies (e.g., SDP051-001) for population PK and PK/PD modelling. The methods and results of that population modelling will be reported separately.

6.8 EXPLORATORY ANALYSES

Modified ACR20, ACR50, ACR70

Modified ACR20, mACR50 and mACR70 include the same components as ACR20, ACR50 and ACR70, except excludes the acute-phase reactants, i.e. CRP. Therefore a mACR50 is based on at least a 50% improvement in TJC and SJC as well as two of the four remaining criteria; similarly 20% improvement is used for mACR20 and 70% improvement for mACR70 ([Greenburg et al 2009](#)).

The proportion of mACR20/mACR50/mACR70 responders at Week 12 and Week 24 will be summarized descriptively using the efficacy analysis population.

Patients who withdraw from the study prior to the Week 12 ACR assessment, and all patients in whom the Week 12 mACR20/mACR50/mACR70 response cannot be determined for any reason, will be considered non-responders for the summaries of mACR20/mACR50/mACR70. Similarly missing mACR20/mACR50/mACR70 at Week 24 will be imputed with non-responder status.

Short-form Health Survey (SF-36v2)

The SF-36v2 is a self-completed questionnaire described in Section [4.6.1.12](#).

The change from Baseline in SF-36v2 mental component score (MCS) and physical component score (PCS) at Week 12 and Week 24 will be summarized descriptively by treatment/dose arm using the efficacy analysis population.

No imputation for missing MCS or PCS will be performed.

Brief Fatigue Inventory (BFI)

The BFI is a self-completed PRO questionnaire described in Section [4.6.1.12](#).

The change from Baseline in BFI items 2, 3 and 4, as well as total score will be summarized descriptively at Week 12 and Week 24 by treatment/dose arm using the efficacy analysis population.

No imputation for missing BFI scores will be performed.

Patient and Physician VAS items

In addition to being included in composite RA disease scores, the PtGA VAS and PGA VAS will be presented individually to describe, respectively, the patient and physician global assessment of disease activity changes from baseline at Week 12 and Week 24 using the efficacy analysis population.

The PtPA VAS change from baseline at Week 12 and Week 24 will also be presented using the efficacy analysis population.

PtGA, PGA and PtPA VAS changes from baseline will be summarized descriptively.

Missing PtGA and PtPA scores will not be imputed.

Potentially Prognostic and Disease Severity Biomarkers

The potentially prognostic and disease severity biomarkers (MBDA and CTX-II, Section 3.2.5) will be summarized descriptively at Baseline by treatment/dose arm. In addition, the synovium cadherin-11 *data*, synovial fluid *and* blood soluble cadherin-11 data will be summarized descriptively by visit and treatment/dose arm. Those biomarkers will be summarized using the efficacy analysis population.

The relationship between the potentially prognostic and disease severity biomarkers and efficacy endpoints will also be analyzed and reported descriptively.

Bone remodeling and cartilage markers

Bone remodeling and cartilage markers (including but not limited to CTX-1, PINP and osteocalcin) will be summarized descriptively by visit and treatment/dose arm. Those biomarkers will be summarized using the efficacy analysis population.

The relationship between the markers mentioned above and efficacy endpoints will also be analyzed and reported descriptively.

Safety Biomarkers

The safety biomarkers (T cells, B cells, NK cells, granulocyte and monocyte markers, Section 3.2.5) will be summarized descriptively by visit and treatment/dose arm using the safety analysis population.

Disease activity as assessed by MRI (Part 2 only)

The OMERACT RA MRI scoring system (RAMRIS) will be used for the evaluation of inflammatory and destructive changes in RA hands and wrists at baseline, Week 12 and Week 24 (Ostergaard et al 2003). In addition, the CARLOS method will be used to

assess cartilage loss ([Peterfy et al 2012](#)), and total damage and total inflammation scores will be calculated ([Peterfy et al 2016](#)).

The change from baseline in synovitis, osteitis, bone erosions, bone marrow edema, cartilage loss, total damage and total inflammation will be summarized descriptively by visit and treatment arm using the efficacy analysis population.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses

An interim analysis of the primary efficacy outcome measure (ACR50 at Week 12) will be carried out after the first 50% of the patients within Part 2 of the study have completed their Week 12 assessment visit. The data will be reviewed by the IMC and SOC.

The difference in ACR50 response rate at Week 12 between the RO7123520 810 mg dose group and the placebo group will be compared descriptively. If no difference between the treatment arms is observed for ACR50 (i.e., the difference is $\leq 0\%$) then, the study may be stopped for futility. If a positive difference is observed then, the Sponsor will determine whether to start Part 3 of the study at this point (also continuing Part 2 recruitment until completion) or wait until all of the Part 2 patients have been recruited and have completed the Week 12 visit, where the decision will be revisited.

Once all of the patients in Study Part 3 have completed their Week 12 visit, a data snapshot will be taken for the purpose of the dose-response analysis (Section [6.6.2](#)). The study will not be modified at this point and will continue until all patients have completed the final follow-up visit.

6.9.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two additional interim efficacy analyses (i.e., beyond what is specified in Section [6.9.1](#)). The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the EDC system.

A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the investigator.

The Sponsor will produce a Data Handling Manual and a Data Management Plan that describe the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an on line Electronic Data Capture (EDC) system. The data collected in the source documents is entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each Patient enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. If a Patient withdraws from the study, the reason must be noted on the eCRF. If a Patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor/CRO in the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor/CRO and should be handled in accordance with instructions from the Sponsor/CRO.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an electronic device to capture PRO data. The data will be transmitted to a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The Investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section [7.6](#).

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that

period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S.

Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section [9.5](#)).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

Roche shall also submit an Development Safety Update Report (DSUR) once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

It is the understanding of the sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an Institutional Review Board (IRB). This board must operate in accordance with the current Federal Regulations. The sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments /modifications are made to the protocol. Roche shall also submit an IND Annual Report to FDA according to local regulatory requirements and timelines.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

Vendors for the IxRS, the MRI reading and the ePRO management will be selected. The Site Management is outsourced to [REDACTED] UK. [REDACTED] will manage the samples centrally.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

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Appendix 1 Schedule of Assessments for Parts 1, 2 and 3 (without Extension)

Week	Screening	Screening	Baseline	Week 1 ^{a,b}	Week 2	Week 3 ^a	Week 4	Week 5 ^a	Week 6 ^a	Week 8	Week 9 ^a	Week 10	Week 12 ^c	Week 16 ^d	Week 24 ^k	Early Termination Safety Visit
Day	D-28 to D-7	D-7 to D-1	Day 1	0	24	312	336	648	672	984	1320	1344	1656	1992	2664	4008
Time Relative (h)					+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3
Visit Window	notime															
Assessments	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****	*****
Informed Consent	X															
Demography	X															
Medical History	X		X													
Substance Use	X															
Inclusion/Exclusion	X															
Randomisation				X												
SF-36 v2 ^e					X									X		
HAQ-D ^c					X		X		X		X			X	X	X
BFI ^e					X									X		
Patient's Global Assessment of Pain (PtPA) ^e						X		X		X		X		X	X	X
Patient Global Assessment of Disease Activity (PtGA) ^e	X					X		X		X		X		X	X	X
Morning Stiffness ^e						X		X		X		X		X	X	X
Physical Examination ⁱ	X			X	X	X	X	X	X	X	X	X		X	X	X
Skin Examination (incl. foot soles and palms of the hand)	X			X	X	X	X	X	X	X	X		X	X	X	X
Vital Signs ^f	X			5	X	5	X	5	X	X	5	X		X	X	X
ECG-12 Lead (Triplicate)	X				X		X		X		X			X	X	X
Bone Mineral Density (Lumbar Spine L1-L4)				X										X		
MRI Scan ^g				X										X		
Hematology	X			X		X		X		X		X		X	X	X
Blood Chemistry	X			X		X		X		X		X		X	X	X
Coagulation	X			X		X		X		X		X		X	X	X
Lipids	X			X		X		X		X		X		X	X	X
Serology	X															
Serum Pregnancy Test	X															
Urine Pregnancy Test				X		X		X		X		X		X	X	X
Urinalysis	X			X		X		X		X		X		X	X	X
Rheumatoid Factor	X			X		X		X		X		X		X	X	X
ACPA	X			X				X			X			X	X	X
HsCRP	X			X		X		X		X		X		X	X	X
ESR (Westergren method) ^h	X			X		X		X		X		X		X	X	X
Immunoglobulin Levels (IgG/A/M)				X				X						X	X	X
PK RO7123520 (Synovial Fluid) ⁱ				X										X		
Synovial Fluid for RNA Profiling ⁱ				X										X		
Synovial Fluid for PD Biomarkers ⁱ				X										X		
Synovial Biopsies for RNA Profiling ⁱ				X										X		
Synovial Biopsies ⁱ				X										X		
PK RO7123520 (Serum)				2		2		2						X	X	X
Anti-Drug Antibody (ADA)				X										X		X
Serum Sampling for PD Biomarkers				X				X						X		
Plasma Sampling for PD Biomarkers				X				X						X		
Urine Sampling for PD Biomarkers				X				X						X		
Whole Blood (RNA) Sampling for RBR				X										X		
Whole Blood (DNA) Sampling for RBR				X										X		
Serum Sampling for RBR				X										X		
Plasma Sampling for RBR				X										X		
Safety Biomarkers (blood cell markers)				X		X		X		X				X	X	X
Bone Biomarkers (CTX-1, PINP, osteocalcin)				X				X						X	X	X
Swollen/Tender Joint Count (66/68 joints) ^g	X			X		X		X		X		X		X	X	X
Physician Global Assessment of Disease Activity (PGA) ^e				X		X		X		X		X		X	X	X
Administration of Study Medication				X		X		X				X				
Safety Follow-up Phone Call										X			X			
Adverse Events											X					
Previous and Concomitant Treatments											X					

Appendix 1 Schedule of Assessments for Parts 1, 2 and 3 (without Extension) (cont.)

- a **Part 1 only:** Assessments performed in Part 1.
- b **Part 2:** Overnight stay required following first dose for the first 15 subjects.
- c Efficacy and safety assessments for patients who do not enter the Extension Phase.
- d Follow up for patients who do not enter the Extension Phase.
- e Questionnaires are self-administered before the patient receives any information on disease status, prior to the performance of non-PRO and ClinRO assessments, and prior to the administration of study treatment, unless otherwise specified. Collected using ePRO device or paper PRO.
- f Vital signs at the start of the infusion, every 15 minutes during the infusion, and then at the end of infusion.
- g **Part 2 only:** MRI of the hand including wrist, contrast-enhanced, RA of hands need to be queried first.
- h All sites must do this locally.
- i Optional assessment; performed at selected centers only.
- j Performed in **Part 1** and **Part 2** only.
- k German sites only.
- l *Physical examination may include an extended examination (i.e., symptom-directed, as clinically indicated) as per Investigator's discretion.*

Appendix 1 Schedule of Assessments Detail for Part 1, 2 and 3 (without Extension) (cont.)

Week	Day	Scheduled Time (h)	Vital Signs	ECG-12 Lead (Triplicate)	HsCRP	Safety Biomarkers (blood cell markers)	Bone Biomarkers (CTX-1, PINP, osteocalcin)	PK RO7123520 (Synovial Fluid) ^a	Synovial Fluid for RNA Profiling ^a	Synovial Fluid for PD Biomarkers ^a	Synovial Biopsies for RNA Profiling ^a	Synovial Biopsies ^a	PK RO7123520 (Serum)	Anti-Drug Antibody (ADA)	Serum Sampling for PD Biomarkers	Plasma Sampling for PD Biomarkers	Urine Sampling for PD Biomarkers	MRI Scan ^b	Whole Blood (RNA) Sampling for RBR	Whole Blood (DNA) Sampling for RBR	Serum Sampling for RBR	Plasma Sampling for RBR
Screening	D-28 to D-7		x	x	x																	
	D-7 to D-1																	x				
Baseline		Predose	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
		0.25	x																			
		0.5	x																			
		0.75	x																			
		EOI	x																			
		EOI +1										x										
Week 1	Day 2		x																			
		Predose	x	x	x	x							x									
		0.25	x																			
		0.5	x																			
		0.75	x																			
		EOI	x																			
		EOI +1										x										
Week 2	Day 14																					
Week 3	Day 15		x																			
		Predose	x	x	x	x	x						x		x	x	x	x				
		0.25	x																			
		0.5	x																			
		0.75	x																			
		EOI	x										x									
		EOI +1																				
Week 4	Day 28																					
Week 5	Day 29		x																			
Week 6	Day 42		x	x	x	x							x									
Week 8	Day 56																					
													x									
													x									
Week 9	Day 57		x																			
Week 12	Day 84		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Week 16	Day 112		x	x	x	x	x	x					x	x								
Week 24 ^c	Day 168		x																			
Early Termination Safety Visit			x	x	x	x	x	x					x	x								

a Optional assessment; performed at selected centers only.

b **Part 2 only:** MRI of the hand including wrist, contrast-enhanced, RA of hands needs to be queried first.

c German sites only.

Appendix 2 Schedule of Assessments for Optional Extension for Parts 1, 2 and 3

Week	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 28	Week 36 ^g	Early Termination Safety Visit
Day	Day 84	Day 98	Day 112	Day 126	Day 140	Day 154	Day 168	Day 196	Day 252	
Time Relative (h)	1992	2328	2664	3000	3336	3672	4008	4680	6024	
Visit Window	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	
Assessments	██████████	██████████	██████████	██████████	██████████	██████████	██████████	██████████	██████████	
Informed Consent	X									
SF-36 v2 ^a	X						X			
HAQ-DL ^a	X		X		X		X	X		X
BFI ^a	X						X			
Patient's Global Assessment of Pain (PtPA) ^a	X		X		X		X	X		X
Patient Global Assessment of Disease Activity (PtGA) ^a	X		X		X		X	X		X
Morning Stiffness ^a	X		X		X		X	X		X
Physical Examination ^h	X		X		X		X	X		X
Skin Examination (incl. foot soles and palms of the hand)	X		X		X		X	X		X
Vital Signs ^b	5		5		5		X	X		X
ECG-12 Lead (Triplicate)	X		X		X		X	X		X
Bone Mineral Density (Lumbar Spine L1-L4) ^c	X						X			
MRI Scan	X						X			
Hematology	X		X		X		X	X		X
Blood Chemistry	X		X		X		X	X		X
Coagulation	X		X		X		X	X		X
Lipids	X		X		X		X	X		X
Urine Pregnancy Test	X		X		X		X	X		X
Urinalysis	X		X		X		X	X		X
Rheumatoid Factor	X		X		X		X	X		X
ACPA	X							X		X
HsCRP ^d	X		X		X		X	X		X
ESR (Westergren method)	X		X		X		X	X		X
Immunoglobulin Levels (IgG/A/M)	X						X	X		X
PK R07123520 (Synovial Fluid) ^e	X						X			
Synovial Fluid for RNA Profiling ^e	X						X			
Synovial Fluid for PD Biomarkers ^e	X						X			
Synovial Biopsies for RNA Profiling ^e	X						X			
Synovial Biopsies ^e	X						X			
PK R07123520 (Serum)	2		2		2		X	X		X
Anti-Drug Antibody (ADA)	X							X		X
Serum Sampling for PD Biomarkers	X		X				X	X		X
Plasma Sampling for PD Biomarkers	X		X				X	X		X
Urine Sampling for PD Biomarkers	X		X				X	X		X
Safety Biomarkers (blood cell markers)	X		X				X	X		X
Bone Biomarkers (CTX-1, PINP, osteocalcin)	X		X				X	X		X
Swollen/Tender Joint Count (66/68 joints) ^a	X		X		X		X	X		X
Physician Global Assessment of Disease Activity (PGA) ^a	X		X		X		X	X		X
Administration of Study Medication	X		X		X					
Safety Follow-up Phone Call ^f		X		X		X				
Adverse Events							X			
Previous and Concomitant Treatments							X			

Appendix 2 Schedule of Assessments for Optional Extension for Parts 1, 2 and 3 (cont.)

- a Questionnaires are self-administered before the patient receives any information on disease status, prior to the performance of non-PRO and ClinRO assessments, and prior to the administration of study treatment, unless otherwise specified. Collected using ePRO device or paper PRO.
- b Vital signs at the start of the infusion, every 15 minutes during the infusion, and then at the end of infusion.
- c **Part 2 only:** MRI of the hand including wrist, contrast-enhanced, RA of hands need to be queried first.
- d All sites must do this locally.
- e Optional assessment; performed at selected centers only.
- f Performed in **Part 1** and **Part 2** only.
- g German sites only.
- h *Physical examination may include an extended examination (i.e., symptom-directed as clinically indicated) as per Investigator's discretion.*

Appendix 2 Schedule of Assessments Detail for Optional Extension for Parts 1, 2 and 3 (cont.)

Week	Day	Scheduled Time (h)	Vital Signs	ECG-12 Lead (Triplicate)	HsCRP	Safety Biomarkers (blood cell markers)	Bone Biomarkers (CTX-1, PINP, osteocalcin)	PK RO7123520 (Synovial Fluid) ^a	Synovial Fluid for RNA Profiling ^a	Synovial Fluid for PD Biomarkers ^a	Synovial Biopsies for RNA Profiling ^a	Synovial Biopsies ^a	PK RO7123520 (Serum)	Anti-Drug Antibody (ADA)	Serum Sampling for PD Biomarkers	Plasma Sampling for PD Biomarkers	Urine Sampling for PD Biomarkers	MRI Scan ^b
Week 12	Day 84	Predose	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
		0.25	x															
		0.5	x															
		0.75	x															
		EOI	x															
		EOI +1										x						
Week 16	Day 112	Predose	x	x	x	x	x						x		x	x	x	
		0.25	x															
		0.5	x															
		0.75	x															
		EOI	x															
		EOI +1										x						
Week 20	Day 140	Predose	x	x	x								x					
		0.25	x															
		0.5	x															
		0.75	x															
		EOI	x															
		EOI +1										x						
Week 24	Day 168		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Week 28	Day 196		x	x	x	x	x					x	x	x	x	x	x	
Week 36 ^c	Day 252		x															
Early Termination Safety Visit			x	x	x	x	x					x	x	x	x	x		

a Optional assessment; performed at selected centers only.

b **Part 2 only:** MRI of the hand including wrist, contrast-enhanced, RA of hands needs to be queried first.

c German sites only.

Appendix 3 Visual Analogue Scale Patient Global Assessment of Disease Activity (PtGA)

Considering all the ways your rheumatoid arthritis affects you, how are you feeling today?



Appendix 4 Visual Analogue Scale Physician Global Assessment of Disease Activity (PGA)

Considering all the aspects of the patient's current disease activity, how do you rate them at this time?

Very well _____ **Very Poorly**

**Appendix 5 Visual Analogue Scale
Patient's Global Assessment of Pain (PtPA)**

My pain due to my rheumatoid arthritis at this time is:

No _____ Most Severe
Pain _____ Pain

Appendix 6 Health Assessment Questionnaire (HAQ-DI)

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
<u>DRESSING & GROOMING</u>				
Are you able to:				
Dress yourself, including shoelaces and buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>ARISING</u>				
Are you able to:				
Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>EATING</u>				
Are you able to:				
Cut your own meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>WALKING</u>				
Are you able to:				
Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

<input type="checkbox"/> Devices used for Dressing (button hook, zipper pull, etc.)	<input type="checkbox"/> Built up or special utensils	<input type="checkbox"/> Crutches
	<input type="checkbox"/> Cane	<input type="checkbox"/> Wheelchair
<input type="checkbox"/> Special or built up chair	<input type="checkbox"/> Walker	

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

<input type="checkbox"/> Dressing and grooming	<input type="checkbox"/> Arising	<input type="checkbox"/> Eating	<input type="checkbox"/> Walking
--	----------------------------------	---------------------------------	----------------------------------

Appendix 6 Health Assessment Questionnaire (HAQ-DI) (cont.)

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
<u>HYGIENE</u>				
Are you able to:				
Wash and dry your body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Take a tub bath?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get on and off the toilet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>REACH</u>				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bend down to pick up clothing from the floor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>GRIP</u>				
Are you able to:				
Open car doors?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open previously opened jars?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turn faucets on and off?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>ACTIVITIES</u>				
Are you able to:				
Run errands and shop?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of a car?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do chores such as vacuuming or yard work?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

<input type="checkbox"/> Raised toilet seat	<input type="checkbox"/> Bathtub bar	<input type="checkbox"/> Long-handled appliances for reach
<input type="checkbox"/> Bathtub seat	<input type="checkbox"/> Long-handled appliances in bathroom	<input type="checkbox"/> Jar opener (for jars previously opened)

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

<input type="checkbox"/> Hygiene	<input type="checkbox"/> Reach	<input type="checkbox"/> Gripping and opening things	<input type="checkbox"/> Errands and chores
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Appendix 6 Health Assessment Questionnaire (HAQ-DI) (cont.)

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY MOSTLY MODERATELY A LITTLE NOT AT ALL

Your PAIN: How much pain have you had IN THE PAST WEEK?

On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

<input type="text"/>	<input type="text"/>	<input type="text"/>
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Appendix 7 Short-form Health Survey (SF-36v2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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Appendix 7 Short-form Health Survey (SF-36v2) (cont.)

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3

c. Lifting or carrying groceries 1 2 3

d. Climbing several flights of stairs 1 2 3

e. Climbing one flight of stairs 1 2 3

f. Bending, kneeling, or stooping 1 2 3

g. Walking more than a mile 1 2 3

h. Walking several hundred yards 1 2 3

i. Walking one hundred yards 1 2 3

j. Bathing or dressing yourself 1 2 3

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Appendix 7 Short-form Health Survey (SF-36v2) (cont.)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
				

- a Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5
- d Had difficulty performing the work or other activities (for example, it took extra effort) 1..... 2..... 3..... 4..... 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

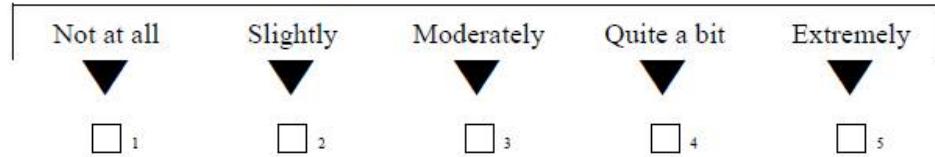
All of the time	Most of the time	Some of the time	A little of the time	None of the time
				

- a Cut down on the amount of time you spent on work or other activities 1..... 2..... 3..... 4..... 5
- b Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c Did work or other activities less carefully than usual 1..... 2..... 3..... 4..... 5

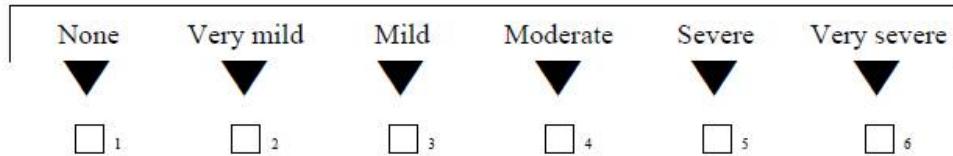
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Appendix 7 Short-form Health Survey (SF-36v2) (cont.)

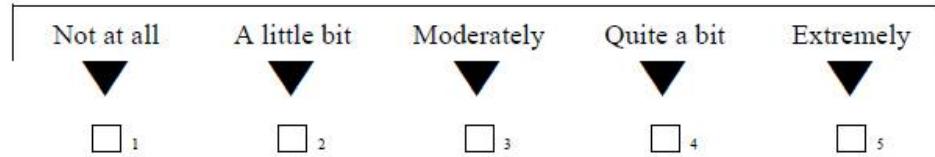
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much body pain have you had during the past 4 weeks?



8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?



Appendix 7 Short-form Health Survey (SF-36v2) (cont.)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
f Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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Appendix 7 Short-form Health Survey (SF-36v2) (cont.)

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼

- a I seem to get sick a little easier than other people 1..... 2..... 3..... 4..... 5
- b I am as healthy as anybody I know 1..... 2..... 3..... 4..... 5
- c I expect my health to get worse 1..... 2..... 3..... 4..... 5
- d My health is excellent..... 1..... 2..... 3..... 4..... 5

Thank you for completing these questions!

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Appendix 8 Brief Fatigue Inventory (BFI)

Brief Fatigue Inventory											
STUDY ID# <input type="text"/>						HOSPITAL# <input type="text"/>					
Date: <input type="text"/> / <input type="text"/> / <input type="text"/>		Time: <input type="text"/>									
Name: <input type="text"/> <input type="text"/> <input type="text"/>		Last <input type="text"/>			First <input type="text"/>			Middle Initial <input type="text"/>			
Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes <input type="checkbox"/> No <input type="checkbox"/>											
1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.											
0	1	2	3	4	5	6	7	8	9	10	As bad as you can imagine
No Fatigue											
2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.											
0	1	2	3	4	5	6	7	8	9	10	As bad as you can imagine
No Fatigue											
3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.											
0	1	2	3	4	5	6	7	8	9	10	As bad as you can imagine
No Fatigue											
4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal work (includes both work outside the home and daily chores)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
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Appendix 9 Swollen/tender joint count (SJC/TJC)

The joints to be evaluated for tenderness (68) and swelling (66) consist of the following:

- Temporomandibular joint
- Sternoclavicular joint
- Acromioclavicular joint
- Shoulders ^a
- Elbows ^a
- Wrists ^a
- Interphalangeal on digit 1 ^a
- Distal interphalangeal joints on digits 2–5
- Proximal interphalangeal joints on digits 2–5 ^a
- Metacarpophalangeal joints on digits 1–5 ^a
- Hips (tenderness only)
- Knees ^a
- Ankles
- *Tarsus*
- Metatarsophalangeal joints on toes 1–5
- Interphalangeal joints on toes 1–5

^a Includes the 28 joints used to calculate the Disease Activity Score (DAS)28

Appendix 10 Assessment of Morning Stiffness

Please indicate the duration of morning stiffness experienced yesterday (duration in hours and minutes).

<input type="text"/> 	Hrs	<input type="text"/> 	Mins
--	-----	--	------