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|---|---|
| **Official Title:** | Prospective, multicentre, placebo-controlled, double-blind interventional study to compare the efficacy of maintenance treatment with Tocilizumab with or without Glucocorticoid discontinuation in rheumatoid arthritis patients |
| **NCT Number:** | NCT02573012 |
| **Document Dates:** | Protocol Amendment/Version 3: 22-Jun-16 |

# PROTOCOL

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| **TITLE:** | **PROSPECTIVE, MULTICENTRE, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY OF MAINTENANCE TREATMENT WITH TOCILIZUMAB WITH OR WITHOUT GLUCOCORTICOID DISCONTINUATION IN RHEUMATOID ARTHRITIS PATIENTS** |
| **PROTOCOL NUMBER:** | MA29585 |
| **VERSION NUMBER:** | 3.0 |
| **EUDRACT NUMBER:** | 2014-004673-16 |
| **TEST PRODUCT:** | Tocilizumab, prednisone |
| **MEDICAL MONITOR:** | [redacted] M.D. |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | Version 1.0: 30-Mar-2015 |
| **DATE AMENDED:** | Version 2.0: 05-Jun-2015<br>Version 2.1: 22-Jun-2015<br>Version 3.0: See electronic date stamp below |

## PROTOCOL AMENDMENT APPROVAL

| Approver's Name | Title | Date and Time (UTC) |
|---|---|---|
| [redacted] | [redacted] | 22-Jun-2016 14:27:28 |

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| **TITLE:** | **PROSPECTIVE, MULTICENTRE, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY OF MAINTENANCE TREATMENT WITH TOCILIZUMAB WITH OR WITHOUT GLUCOCORTICOID DISCONTINUATION IN RHEUMATOID ARTHRITIS PATIENTS** |
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| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

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

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local Study Monitor.

## PROTOCOL SYNOPSIS

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|---|---|
| **TITLE:** | **PROSPECTIVE, MULTICENTRE, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY OF MAINTENANCE TREATMENT WITH TOCILIZUMAB WITH OR WITHOUT GLUCOCORTICOID DISCONTINUATION IN RHEUMATOID ARTHRITIS PATIENTS** |
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| **EUDRACT NUMBER:** | 2014-004673-16 |
| **TEST PRODUCT:** | Tocilizumab, prednisone |
| **PHASE:** | IIIb/IV |
| **INDICATION:** | Rheumatoid Arthritis |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

### I. Objectives

**Efficacy Objectives**

- To compare the impact on disease activity of continued vs. tapered prednisone in RA patients with stable low disease activity (LDA; defined as a Disease Activity Score [DAS28]-erythrocyte sedimentation rate [ESR] score ≤ 3.2), as assessed by the change in DAS28 ESR score between randomization and Week 24 post-randomization.

The key secondary efficacy objective for this study is as follows:

- To compare the proportion of patients who continue vs. taper prednisone with LDA (DAS28 ESR score ≤ 3.2) at Week 24 post-randomization, who have not suffered a flare due to rheumatoid arthritis (RA) and who showed no confirmed adrenal insufficiency requiring replacement therapy.

Other secondary efficacy objectives for this study are as follows:

- To compare, between patients who continue vs. taper prednisone:
  - changes in disease activity measures, such as clinical disease activity index (CDAI) and simplified disease activity index (SDAI) from randomization to Week 24 post-randomization
  - the proportion of patients with ≥ 1 RA flare, the time to first RA flare and the number of RA flares
  - the proportion of patients with ≥ 1 administration of RA flare rescue medication, the time to first administration, and the number of administrations of RA flare rescue medication

- cumulative prednisone exposure (dose) between randomization and Week 24 post-randomization
- the proportion of patients who maintain LDA (DAS28 ESR score ≤ 3.2) and the proportion of patients who maintain the baseline disease activity level at Week 24 post-randomization
- proportion of patients who permanently discontinue study treatment due to insufficient RA flare control
- changes in the ACR core set from randomization to post-randomization Week 24
- to identify predictors of successful prednisone dose-tapering at Week 24 post-randomization.

**Safety Objectives**

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of tocilizumab (TCZ) during the randomized phase of the study, based on an assessment of adverse events (AEs), vital signs, physical examination and clinical laboratory tests, including immunogenicity, in patients with rheumatoid arthritis who continue vs taper prednisone.
- To describe the safety of the proposed prednisone-tapering scheme.

For further details on study objectives, refer to Section 2.3 (Patient-reported outcome objectives), and Section 2.4 (Exploratory objectives).

## II. Study Design

**Description of Study**

This is a Phase IIIb/IV, two-arm, randomized, double-blind, placebo-controlled, parallel-group, international, multicentre trial. The primary study objective is to compare the change in disease activity (as assessed by DAS28 ESR) from randomization to Week 24 post-randomization, in patients with stable LDA (DAS28 ESR score ≤ 3.2) who have been randomized to either continue or taper prednisone in a double-blinded fashion. Patients can enter and be randomized into this study via two tracks. In order to reach the randomization target of 226 patients, between 240 and 450 patients are planned to be recruited via both tracks in parallel over an approximately 1-year period. Given that the randomization ratio will differ between the two tracks, recruitment of patients into the two tracks will be steered to achieve the randomization target without exceeding the total number of 450 recruited patients. A Steering Committee will oversee the general conduct of the study. An independent Data Monitoring Committee (iDMC) will share responsibility for evaluating the safety of the patients participating in the trial at regular intervals throughout the study.

See Figure 1 for an overview of the study design.

*Track TCZ-experienced patients*

This track consists of patients who received TCZ for at least 24 weeks prior to randomization, either subcutaneously (SC), at a dose of 162 mg once a week (QW) or intravenously (IV), at a dose of 8 mg/kg every 4 weeks (Q4W), not exceeding 800 mg/dose.

Furthermore, eligible patients must have received 5 – 15 mg/day oral prednisone (or glucocorticoid [GC] equivalent) for at least 20 weeks prior to the Screening Visit, and they must

be on 5 mg/day oral prednisone (or GC equivalent) at the Screening Visit. Eligible patients must also have a DAS28 ESR score ≤ 3.2 at the Screening Visit; see below for a complete list of eligibility criteria.

The Screening Visit for *TCZ-experienced* patients occurs up to 6 weeks prior to randomization.

*TCZ-experienced* patients will be switched to Sponsor-provided open-label prednisone 5 mg/day after signed informed consent, and as per Section 4.3.2.2.

Patients on conventional synthetic disease modifying anti-rheumatic drug (csDMARD) therapy at the Screening Visit should be maintained on this therapy until the end of the study, and no new csDMARD may be initiated after the patient has signed the informed consent. Modification of stable csDMARD therapy is restricted, as per Section 4.4.1.1.

Oral and other systemic glucocorticoids not provided by the Sponsor are forbidden after signed informed consent. Intra-articular or parenteral glucocorticoids are forbidden within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone); see Section 4.3.2.2 for specific instructions.

During the Screening Period, other analgesics and anti-inflammatory drugs (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) are allowed. If clinically feasible and safe, investigators should encourage patients to withhold these drugs for 12-24 hours prior to the randomization visit at which the baseline efficacy assessments are conducted; see Section 4.4.1.2 for specific instructions.

*TCZ-experienced* patients will be randomized if they meet all randomization criteria as per Section 4.5.10.

See Figure 2 for a graphical representation of the study design, emphasizing the pre-randomization period for *Track TCZ-experienced* patients.

*Track TCZ-naïve patients*

This track consists of patients who have not received any prior treatment with TCZ, or whose previous TCZ treatment occurred > 12 months prior to screening, and TCZ was not discontinued due to lack of efficacy, side effects, or any other safety concerns. At the Screening Visit, eligible patients must have active RA defined as DAS28 ESR > 3.2, must be considered by the investigator as inadequate responders to csDMARDs or biological disease-modifying antirheumatic drugs (bDMARDs), and must be receiving oral prednisone 5 to 15 mg/day (or GC equivalent). Patients fulfilling all eligibility criteria will be enrolled in the 24-week Lead-in Phase, during which time they will receive open-label TCZ SC at a dose of 162 mg QW or open-label TCZ IV at a dose of 8 mg/kg Q4W, not exceeding 800 mg/dose. The choice between TCZ SC or TCZ IV will be made by the investigator, depending on the local availability and individual patient acceptance and tolerability of the SC formulation.

During the open-label Lead-in Phase, the dose of prednisone (or GC equivalent) will be tapered down to prednisone 5 mg/day (if clinically feasible) according to a scheme determined by the investigator.

**All patients who are not on prednisone 5 mg/day (or GC equivalent) at the open-label Lead-in Week 20 Visit will be withdrawn from the study.**

Patients who are on prednisone 5 mg/day (or GC equivalent) at the open-label Lead-in Week 20 Visit will be treated the following way:

- **Patients with a DAS28 ESR ≤ 3.2** at the Lead-in Week 20 Visit will be switched to Sponsor-provided open-label prednisone 5 mg/day for an additional 4 weeks. Patients on

csDMARD therapy at the Lead-in Week 20 Visit should be maintained on this therapy until the end of the study, and no new csDMARD may be initiated after this visit. Modification of stable csDMARD therapy is restricted, as per Section 4.4.1.1.

- **Patients with a DAS28 ESR > 3.2** at the Lead-in Week 20 Visit will be withdrawn from the study, unless they have improved considerably, defined as a DAS28 ESR score < 4.4 and a change in DAS28 ESR score ≥ 1.2 compared to baseline. **Considerably improved patients** at Lead-in Week 20 (DAS28 ESR score > 3.2 and < 4.4 and a change in DAS28 ESR score ≥ 1.2 compared to baseline) may continue TCZ SC and prednisone 5 mg/day (or GC equivalent) treatment for an additional 4 weeks. At the Lead-in Week 24 Visit, patients will be switched to Sponsor-provided open-label prednisone 5 mg/day for an additional 4 weeks if:

  1. They are receiving prednisone 5 mg/day (or GC equivalent), and
  2. DAS28 ESR ≤ 3.2.

  Patients not meeting these two criteria will be withdrawn.

  Patients on csDMARD therapy at the Lead-in Week 24 Visit should be maintained on this therapy until the end of the study, and no new csDMARD may be initiated after this visit. Modification of stable csDMARD therapy is restricted, as per Section 4.4.1.1.

Oral and other systemic glucocorticoids not provided by the Sponsor are forbidden during 4 weeks prior to randomization, but otherwise permitted during the open-label Lead-in Phase. Intra-articular or parenteral glucocorticoids are forbidden within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone); see Section 4.3.2.2 for specific instructions.

During the Lead-in Phase, other analgesics and anti-inflammatory drugs (e.g. NSAIDs, acetaminophen) are allowed. If clinically feasible and safe, investigators should encourage patients to withhold these drugs for 12-24 hours prior to visits at which efficacy assessments are conducted. See Section 4.4.1.2 for specific instructions.

RA flares are treated according to standard clinical practice during the Screening and open-label Lead-in Phase.

See Figure 3 for a graphical representation of the study design, emphasizing the pre-randomization period (including the open-label Lead-in Phase) for *Track TCZ-naïve* patients.

*Track TCZ-naïve* patients will be randomized if they meet all randomization criteria as per Section 4.5.10.

Patients who do not meet the randomization criteria will attend a Study Treatment Discontinuation Visit, followed in 4 weeks by a Safety Monitoring Visit (see Appendix 3). These patients will be subsequently treated outside of the study, according to local clinical practice, at the discretion of the investigator.

Randomization numbers will be generated by Roche or its designee and provided to the Interactive Response System (IxRS). Prior to entering the 24-week double-blind Tapering Phase, patients will be randomly assigned (1:1) to one of two treatment groups, either continuing 5 mg/day of prednisone or tapering prednisone in a double-blinded fashion. It is predicted that approximately 95% of patients entering from *Track TCZ-experienced patients* and 50% of patients entering from *Track TCZ-naïve patients* will be randomized, resulting in approximately 226 randomized patients in total.

*24-week Double-blind Tapering Phase (all patients randomized from the TCZ-experienced and -naïve tracks)*

During the 24-week Tapering Phase, randomized patients will receive double-blinded treatment with either blinded study prednisone 5 mg/day or a blinded study tapering regimen consisting of 1 mg decrements of study prednisone every 4 weeks. Study prednisone will be replaced with increasing amounts of placebo during the tapering. All randomized patients will be treated with open-label TCZ SC (162 mg QW) or TCZ IV (8 mg/kg Q4W, not exceeding 800 mg/dose).

Initiation of new csDMARD is forbidden for all patients. Patients must have their existing csDMARD therapy maintained stable throughout the Tapering phase (see Section 4.4.1.1 for specific instructions):

- csDMARD dose may not be increased;
- csDMARD dose reductions or discontinuation are allowed for safety reasons.

The use of systemic GCs which are not provided by the Sponsor are generally prohibited during the 24-week double-blind Tapering Phase, with the exception of treating or preventing serious illness, particularly serious infections or adrenal insufficiency or crisis (see Section 4.3.2.2 for specific instructions). Other analgesics and anti-inflammatory drugs (e.g. NSAIDs, acetaminophen) are allowed. If clinically feasible and safe, investigators should encourage patients to withhold these drugs for 12-24 hours prior to visits at which efficacy assessments are conducted (see Section 4.4.1.2 for specific instructions).

Patients who successfully complete the Tapering Phase will attend a Study Treatment Discontinuation visit at Week 24, and a Safety Follow-up Visit at Week 28 (see Appendix 2). Patients who prematurely withdraw from treatment during the Tapering Phase will attend a Study Treatment Discontinuation Visit followed in 4 weeks by a Safety Monitoring Visit. These patients will be treated thereafter according to the investigator's discretion and encouraged to attend a study visit at Week 24; see Schedule of Assessments (Appendix 3). Patients who prematurely discontinue study medication will not be replaced.

See Figure 4 for a graphical representation of the study design emphasizing the post-randomization period applicable to all randomized patients from both tracks.

*RA Flare Assessment and Treatment during the 24-week Double-blind Tapering Phase*

During the 24-week Tapering Phase, an RA flare may be detected at any scheduled or unscheduled visit, and is defined as:

- a current DAS28 ESR score > 3.2, and
- an increase in DAS28 ESR score > 0.6 from the randomization visit value.

RA flare assessment and treatment must be conducted according to the instructions in Section 4.5.11.

For a patient experiencing an RA flare, TCZ and study prednisone will continue to be dispensed as planned and the blind maintained. The patient will also receive a 2-week course of RA flare rescue medication, consisting of 5 mg/day of Sponsor-provided open-label prednisone. Dose increases to existing csDMARDs or addition of new csDMARDs or any other RA therapy is prohibited (as per Sections 4.4.1 and 4.4.2).

Patients will need to be followed up with a Flare Assessment at the end of the 2-week RA flare rescue medication course. Patients will be determined to have either a resolved RA flare or a second RA flare, according to criteria defined in Section 4.5.11. Patients with persisting RA flares

after treatment of the second flare, will be withdrawn from the study treatment, and followed up and treated as per Appendix 3.

*Safety Follow-up Phase*

Patients completing the 24-week Tapering Phase will undergo a Safety Follow-up Visit 4 weeks after the completion of the Tapering Phase (i.e. at Week 28 post-randomization).

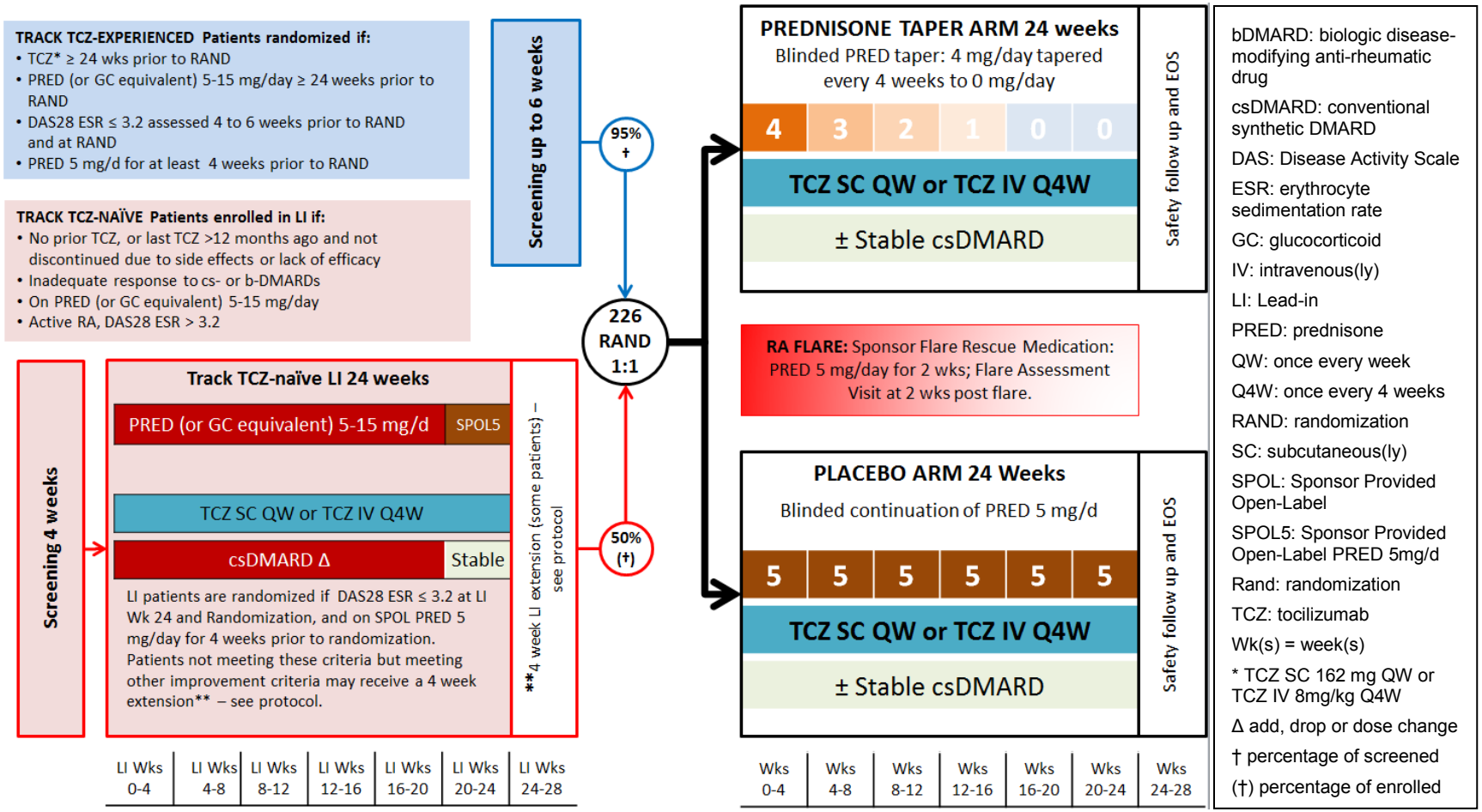
*Post-study Treatment*

Management of patients completing the 24-week Tapering Phase, including treatment of any potential RA flares following completion of study treatment, will be according to local standard clinical practice, at the discretion of the investigator. However, to ensure the scientific integrity of the study and to maintain the blind until database lock, it is recommended that patients completing the 24-week Tapering Phase be treated with open-label 3 mg/day of prednisone and continue TCZ (SC or IV). Higher doses of prednisone, e.g. 5 mg/day may be required in patients who were receiving RA flare rescue medication at Week 24 post-randomization.

The end of the trial is defined as the date of the last visit of the last participating patient in this study. Study unblinding will occur after data base lock, and patients will be subsequently informed as to their previously assigned treatment groups.

A Schedule of Assessments is provided in Appendix 1, Appendix 2, and Appendix 3.

**Figure 1: Study Design**



## III. Number of Patients

Up to 450 patients are expected to be recruited into the study via both tracks in parallel in order to reach 226 randomized patients. About 50% of patients entering from *Track TCZ-naïve patients* are expected to be randomized vs about 95% from *Track TCZ-experienced patients*.

### Target Population

There are two target populations for this study:

- ***Track TCZ-experienced patients:*** Patients with a DAS28 ESR score ≤ 3.2 who are currently receiving TCZ (SC or IV) and 5 mg/day of prednisone (or GC equivalent). Eligibility criteria are evaluated during Screening, which starts up to 6 weeks prior to randomization.
- ***Track TCZ-naïve patients:*** Patients with moderate to severe active RA with an inadequate response to current csDMARD or bDMARD therapy, and who require current treatment with 5 to 15 mg/day of prednisone (or GC equivalent). Following treatment with TCZ and GC taper (if clinically feasible) during the 24-week Lead-Phase, these patients are eligible for randomization if they maintain a DAS28 ESR score ≤ 3.2 and stable prednisone dose of 5 mg/day for 4 weeks prior to randomization. Eligibility criteria are evaluated during Screening, which starts up to 4 weeks prior to enrolment in the Lead-in Phase.

## IV. Eligibility Criteria

### Inclusion Criteria

Patients must meet the following criteria for study entry:

*Track TCZ-experienced patients (study entry is enrolment following randomization):*

1. Able and willing to give written informed consent and comply with the requirements of the study protocol (including treatment on an outpatient basis).
2. Age ≥ 18 years.
3. RA of ≥ 6 months duration diagnosed according to the revised 1987 American College of Rheumatology (ACR, formerly the American Rheumatism Association) criteria or 2010 ACR / EULAR (European League Against Rheumatism) criteria.
4. Have received TCZ either SC (162 mg QW) or IV (8 mg/kg Q4W, not exceeding 800 mg/dose) for the treatment of RA for at least 24 weeks prior to randomization.
5. Have received 5 - 15 mg/day of prednisone (or GC equivalent) for the treatment of RA for at least 20 weeks prior to screening.
6. Currently receiving 5 mg/day of oral prednisone (or GC equivalent) at the Screening Visit.
7. Have a DAS28 ESR score ≤ 3.2 assessed 4 to 6 weeks prior to randomization (assessed at the Screening Visit or a visit prior to the Screening Visit).

*Track TCZ-naïve patients (study entry is enrolment into the lead-in phase):*

1. Able and willing to give written informed consent and comply with the requirements of the study protocol (including treatment on an outpatient basis).
2. Age ≥ 18 years.
3. RA of ≥ 6 months duration diagnosed according to the revised 1987 ACR criteria or 2010 ACR / EULAR (European League Against Rheumatism) criteria.
4. Have active RA (defined as DAS28 ESR score > 3.2).

5. Are considered by the investigator as inadequate responders to csDMARDs or bDMARDs. Are TCZ treatment naïve or last TCZ treatment was > 12 months prior to screening and TCZ was not discontinued due to lack of efficacy, side effects, or any other safety reasons.
6. Are receiving 5 - 15 mg/day prednisone (or GC equivalent) for the treatment of RA.

**Exclusion Criteria**

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

*General*

1. Major surgery (including joint surgery) within 8 weeks prior to screening, or planned major surgery during the study and up to 6 months after randomization.
2. Pregnant women or nursing (breastfeeding) mothers.
3. In females of childbearing potential, a positive serum pregnancy test at screening.
4. Females of childbearing potential unwilling or unable to use a reliable means of contraception (e.g., physical barrier [patient or partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device) during study treatment and for a minimum of 3 months after the last dose of TCZ.
5. Body weight of ≥ 150 kg.
6. Lack of peripheral venous access.

*Disease-related*

7. RA of functional class IV, as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis (see Appendix 7).
8. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, or Felty syndrome). Secondary Sjögren syndrome with RA may be allowed per the discretion of the investigator.
9. Diagnosed with juvenile idiopathic arthritis or juvenile RA and/or RA before the age of 16 years.
10. Prior or current inflammatory joint disease other than RA (e.g., gout, Lyme disease, sero-negative spondyloarthropathy, including reactive arthritis, psoriatic arthritis, arthropathy of inflammatory bowel disease), or prior or current joint infections.
11. Previous history of primary or secondary adrenal insufficiency.

*Previous or Concomitant Prohibited Therapy*

12. Treatment with any investigational agent (tocilizumab excepted) within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening. Treatment with csDMARDs, other DMARDS, and/or biologics for RA which is permanently discontinued within 5 half-lives prior to randomization.
13. Previous treatment with any cell-depleting therapies, including investigational agents or approved therapies (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, anti-CD20).
14. Treatment with IV gamma globulin, plasmapheresis or Prosorba column within 6 months of screening.
15. Intraarticular (IA) or parenteral GCs within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone).

16. Previous treatment with oral or parenteral GCs for conditions other than RA, at any dose used continuously for > 1 week, during the last 1 year prior to screening. Current treatment with topical GC exceeding 20% of body surface area.
17. Immunization with a live/attenuated vaccine within 30 days prior to screening. Patients must agree not to take live attenuated vaccines (including seasonal nasal flu vaccine, varicella vaccine for shingles or chickenpox, vaccines for measles, mumps or rubella without or with varicella [MMR or MMRV], oral polio vaccine and vaccines for yellow fever), within 30 days before the Screening Visit, throughout the duration of the trial and for 60 days following the last dose of study drug.
18. Any previous treatment with alkylating agents such as chlorambucil or with total lymphoid irradiation.

*Laboratory Exclusion Criteria*

19. Inadequate haematological function indicated by any of the following:
    - White blood cells (WBCs) < 3.0 x $10^9$/L (3,000/$mm^3$).
    - Platelet count < 100 x $10^9$/L (100,000/$mm^3$).
    - Haemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L).
    - Absolute neutrophil count (ANC) < 2.0 x $10^9$/L (2,000/$mm^3$).
    - Absolute lymphocyte count < 0.5 x $10^9$/L (500/$mm^3$).
20. Inadequate renal function indicated by serum creatinine > 1.4 mg/dL (> 124 µmol/L) in female patients and > 1.6 mg/dL (> 141 µmol/L) in male patients
21. Inadequate liver function indicated by any of the following:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 times the upper limit of normal (ULN).
    - Total bilirubin > ULN.
22. Positive hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab).

*Previous or Concomitant Conditions*

23. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies.
24. Evidence of current serious uncontrolled cardiovascular (including uncontrolled hyperlipidemia), nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or gastrointestinal (GI) disease.
25. Current liver disease as determined by the investigator.
26. History of diverticulitis, peptic ulcer disease, diverticulosis requiring antibiotic treatment, or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations.
27. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other opportunistic infections (including, but not limited to, tuberculosis [TB] and atypical mycobacterial disease, hepatitis B and C, Epstein-Barr virus, cytomegalovirus and herpes zoster, but excluding fungal infections of nail beds) on the day of enrolment. *Track TCZ-experienced* patients are exempt if they have an active mild infection which does not warrant a treatment interruption as per protocol Section 5.1.1.2 or local standard of care.
28. Neuropathies and/or other conditions that might interfere with pain evaluation (e.g. fibromyalgia) and/or are typically treated with systemic GCs, unless related to primary disease under investigation.

29. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening
30. Active TB requiring treatment within the previous 3 years (patients previously treated for TB with no recurrence within 3 years are permitted). Patients failing to complete the TB evaluation (as per Appendix 9) by the end of screening are excluded.
31. History of or currently active, primary or secondary immunodeficiency.
32. Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including haematological malignancies and solid tumours, except basal and squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix uteri that was excised and cured), or breast cancer diagnosed within the previous 20 years.
33. History of alcohol, drug or chemical abuse within 1 year prior to screening.
34. Pre-existing central nervous system (CNS) demyelination or seizure disorders.
35. Any medical or psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial.

## V. Length of Study

The recruitment phase is expected to last approximately one year. A 24-week Lead-in Phase is required for TCZ-naïve patients. This may be prolonged to 28 weeks in certain cases as defined in the study design section. Patients who are already receiving TCZ will undergo a 4 to 6-week-screening. Both inclusion tracks will last 28 weeks after randomization.

## VI. End of Study

The end of the trial is defined as the date of the last visit of the last participating patient in this study. This is expected to occur 28 weeks after the last patient has been randomized into the study.

## VII. Outcome Measures

### Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Change in DAS28 ESR between randomization and Week 24 post-randomization. DAS28 ESR is a composite score based on tender and swollen 28-joint count, patient's assessment of global status and ESR.

The key secondary efficacy outcome measure for this study is as follows:

- The proportion of patients with LDA (DAS28 ESR score ≤ 3.2) at Week 24 post-randomization, who have not suffered a flare due to RA and who showed no confirmed adrenal insufficiency that required replacement therapy.

Other secondary efficacy outcome measures for this study are as follows:

- Change in CDAI / SDAI between randomization and Week 24 post-randomization. The CDAI is composite score based on tender and swollen joint count, and the patient's and physician's assessment of global status. The SDAI includes the components of CDAI as well as C-reactive protein (CRP).
- The proportion or patients with ≥ 1 RA flare, the time to first RA flare and the number of RA flares.

- The proportion of patients with ≥ 1 administration of RA flare rescue medication, the time to first administration, and the number of administrations of RA flare rescue medication.
- Cumulative prednisone exposure (dose) between randomization and Week 24 post-randomization.
- The proportion of patients who maintain LDA (DAS28 ESR score ≤ 3.2) and the proportion of patients who maintain the baseline disease activity level at Week 24 post-randomization.
- The proportion of patients who permanently discontinue study treatment due to insufficient RA flare control.
- Changes in the ACR core set from randomization to post-randomization Week 24, including: swollen and tender joint counts; patient's assessment of pain and global status; physician's assessment of global status; Health Assessment Questionnaire – Disability Index (HAQ-DI); and acute phase reactants (high sensitivity C-reactive protein [hsCRP] and erythrocyte sedimentation rate [ESR]).

**Safety Outcome Measures**

The safety outcome measures for this study are as follows:

- Nature, frequency and severity of AEs (graded according to CTCAE v4.0) including non-serious and serious adverse events (SAEs), and AEs of special interest.
- Changes in vital signs, physical findings, and clinical laboratory results during and following TCZ administration.
- Assessment of immunogenicity: Immunogenicity sampling will be "event-driven"; for patients who experience a hypersensitivity reaction (including anaphylaxis), additional samples will be taken and tested for anti-TCZ antibodies, plasma TCZ levels (PK) and sIL-6R (PD) at time of event and 8 weeks after the event, as part of the standard immunogenicity sampling protocol. No immunogenicity sampling is required in case of injection site reactions.
- Proportion of patients with confirmed adrenal insufficiency that required replacement therapy.

**Patient-Reported Outcome Measures**

The PRO outcome measures for this study include the following:

- RAID score (measured at enrolment (*Track TCZ-naïve patients* only), randomization and at Week 24 post-randomization).
- HAQ-DI score (assessed at baseline, randomization and at Week 24 post-randomization).
- Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA) score (assessed at enrolment (*Track TCZ-naïve patients* only), randomization and at Week 24 post-randomization).

**Exploratory Outcome Measures**

The exploratory outcome measures for this study are as follows:

- Levels of biomarkers, including but not limited to bone turnover biomarkers, at relevant time points; see Section 3.4.7 for details.
- Measure of non-inherited biomarkers associated with RA biology and TCZ biology; see Section 3.4.7 for details.

- Change in the modified Homeostasis Model Assessment (HOMA1) from the beginning to the end of the Lead-in Phase (*Track TCZ-naïve patients* only).
- Change in HOMA1 from randomization to the end of the study (Week 24; both tracks).

## VIII. Investigational Medicinal Products

**Tocilizumab**

- *Track TCZ-experienced patients* must have received TCZ (162 mg QW SC or 8 mg/kg Q4W IV, not exceeding 800 mg/dose) for at least 24 weeks prior to randomization. The Randomization Visit should coincide with the date of the next scheduled TCZ dose.
- *Track TCZ-naïve patients* will enter a 24-week Lead-in Phase, during which time they will receive open-label TCZ SC at a dose of 162 mg QW or open-label TCZ IV at a dose of 8 mg/kg Q4W (not exceeding 800 mg/dose) at the investigator's discretion. (Patients eligible for a 4-week extension of the Lead-in Phase, as per Section 3.1, will receive 28 weeks of open-label TCZ). Patients transitioning from a previous bDMARD to TCZ (SC or IV) should receive their first TCZ dose at Lead-in Visit 1, and this visit should coincide with the date of the next scheduled administration of the previous bDMARD. TCZ SC initiation should be performed under the supervision of a qualified healthcare professional.
- *24-week Tapering Phase:* randomized patients will receive open-label TCZ SC (162 mg QW) or TCZ IV (8 mg/kg Q4W, not exceeding 800 mg/dose).
- *Post-study Treatment* will be according to local clinical practice, at the discretion of the investigator. It is recommended that patients completing the 24-week Tapering Phase continue treatment with TCZ (SC or IV).

**Prednisone and Other Systemic Glucocorticoids**

- *Screening: Track TCZ-experienced patients:* Prednisone or GC administered during Screening is non-IMP. Patients are switched to Sponsor-provided open-label 5 mg/day prednisone at the Screening Visit (after signing informed consent, and only if they are currently on oral prednisone 5 mg/day or GC equivalent), and will continue taking Sponsor-provided open-label 5 mg/day prednisone for the duration of the screening period. Patients not on prednisone 5 mg/day (or GC equivalent) at the Screening Visit will have failed screening.
- *Screening and Lead-in Phase: Track TCZ-naïve patients:* Prednisone or GC administered during the Screening or Lead-in phase is non-IMP. Eligible patients must be receiving 5 to 15 mg/day of prednisone (or GC equivalent). Patients will enter a 24-week Lead-in Phase, during which time they will continue their open-label prednisone (or GC equivalent). During the Lead-in Phase, the dose of prednisone will be tapered down to 5 mg/day (if clinically feasible) according to a scheme determined by the investigator. All patients who are not on prednisone 5 mg/day (or GC equivalent) at Lead-in Week 20 are discontinued from the study. Patients on 5 mg/day of prednisone (or GC equivalent) and with a DAS28 ESR score ≤ 3.2 at Lead-in Week 20 must be switched to Sponsor-provided open-label 5 mg/day prednisone for the remainder of the Lead-in period (until Lead-in Week 24 / Randomization Visit). Patients who are on 5 mg/day of prednisone (or GC equivalent) and with a DAS28 ESR score > 3.2 at Lead-in Week 20 are discontinued from the study unless they have improved considerably (DAS28 ESR score < 4.4 and a change in DAS28 ESR score ≥1.2 compared to baseline). Considerably improved patients may continue in the Lead-in Phase and are re-assessed at Lead-in Week 24. If these patients are on 5 mg/day of prednisone (or GC equivalent) and have a DAS28 ESR score ≤ 3.2 at Lead-in Week 24, they must be switched to Sponsor

provided open-label 5 mg/day prednisone for the remainder of the Lead-in period (until Lead-in Week 28 / Randomization Visit).

- *24-week Tapering Phase (Double-blind) - All randomized patients: Study Prednisone*: Study prednisone (defined as active prednisone ± placebo) is IMP. Track TCZ-experienced and Track TCZ-naïve patients randomized to tapered prednisone will receive 4 over-encapsulated tablets throughout the 24 weeks of Tapering Phase, consisting of a tapering dose of study prednisone, starting with 4 mg/day, with decrements of 1 mg every 4 weeks. Patients randomized to continuing prednisone will receive 5 mg/day of study prednisone as 4 over-encapsulated tablets throughout the 24 weeks of Tapering Phase. Study prednisone should be taken in the morning.
- *24-week Tapering Phase - All randomized patients: Flare Rescue Medication*: Prednisone administered as a RA flare rescue medication is non-IMP. Patients experiencing an RA flare during the 24-week Tapering Phase must be treated with Sponsor-provided flare rescue prednisone according to Section 4.5.11. (Note: patients experiencing an RA flare during the Lead-in Phase are treated as per local practice).
- *Non-Sponsor Systemic Glucocorticoid Administration – All Study Phases*:
  - Non-Sponsor systemic GC (i.e. oral prednisone and other systemic GC compounds and formulations not provided by the Sponsor) administration is highly restricted:
    - *All patients:* Intra-articular or parenteral GCs are prohibited within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone); see Exclusion Criteria (Section 4.1.3).
    - *Track TCZ-naïve patients*: Non-Sponsor systemic GC (any route of administration) for any purpose (including RA) must not be used after 4 weeks prior to randomization and throughout the 24-week double-blind Tapering Phase. Only Sponsor-provided Study prednisone or RA flare rescue prednisone (see above) may be used; see Randomization Criteria (Section 4.5.10).
    - *Track TCZ-experienced patients:* Non-Sponsor systemic GC (any route of administration) for any purpose (including RA) must not be used after signed informed consent and throughout the 24-week double-blind Tapering Phase. Only Sponsor-provided Study prednisone or RA flare rescue prednisone (see above) may be used.
  - Short-term non-Sponsor systemic GC is permitted after randomization when deemed necessary for treatment or prevention of serious illness, in particular serious infections and adrenal insufficiency or adrenal crisis (see Appendix 11). This administration will be made according to the medical judgment of the investigator, and should be documented in the eCRFs. This non-Sponsor systemic GC treatment or prevention should be stopped as soon as clinically safe.
- *Post-study Treatment* will be according to local clinical practice at the discretion of the investigator. However, to ensure the scientific integrity of the study and to maintain the blind until database lock, it is recommended that patients completing the 24-week Tapering Phase be treated with open-label 3 mg/day of prednisone equivalent (in addition to TCZ). Higher doses of GC, e.g. 5 mg/day of prednisone equivalent may be required in patients who were receiving RA flare rescue medication at Week 24 post-randomization.

## IX. Statistical Methods

### Primary Analysis

The statistical analysis will assess the difference between the two arms in terms of change in DAS28 ESR from randomization (baseline) to Week 24 post-randomization. The primary analysis population will be the intent-to-treat (ITT) population, which will comprise all randomized patients according to the treatment assigned at randomization. The between-group comparison will be performed based on an analysis of covariance (ANCOVA) model including the baseline DAS28 ESR and the other stratification factors applied at randomization.

For ITT patients who are prematurely withdrawn from treatment during the 24-week Tapering Phase, the DAS28 ESR value at the time of study treatment discontinuation will be used in the analysis. For ITT patients who are on RA flare rescue medication at Week 24 post-randomization, the DAS28 ESR value at the time of rescue medication start will be used in the analysis.

### Determination of Sample Size

This study primarily focuses on estimation rather than formal hypothesis testing. A sample size of 226 randomized patients is expected to provide > 80% power to produce a two-sided 95% confidence interval with a half-width < 0.5 DAS28 ESR units. The calculation is based on a two-sided t-test for a difference between the two arms and assumes a standard deviation of 1.33 units (conservative assumption based on data under stable TCZ treatment) and an analysis in the ITT population.

Differences < 0.6 DAS28 ESR units would be considered of marginal clinical importance. There are no reference data for an accurate assumption regarding the expected between-arm difference, but assuming an observed difference of < 0.25 units (mean disease activity is expected to slightly decrease in the steroid taper arm and to be stable in the placebo-taper arm), the two-sided 95% confidence interval will exclude differences between the two arms > 0.6.

For 226 patients to be randomized, taking into account that approximately 50% of included patients are expected to be "Lead-in failures" (i.e. not meeting the randomization criteria for *Track TCZ-naïve patients*), up to approximately 450 patients will need to be included into the study.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ACR | American College of Rheumatology |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANCOVA | analysis of Co-variance |
| Anti-CCP | anti-cyclic citrullinated peptide antibody |
| AST | aspartate aminotransferase |
| ATA | anti-therapeutic antibody |
| AUC | area under the curve |
| bDMARD | biologic disease-modifying antirheumatic drug |
| BMD | bone mineral density |
| BMI | Body Mass Index |
| BUN | blood urea nitrogen |
| CDAI | clinical disease activity index |
| CI | confidence interval |
| ClinRO | clinician-reported outcome |
| CNS | central nervous system |
| CRO | contract research organization |
| CRP | C-reactive protein |
| csDMARD | conventional synthetic disease-modifying antirheumatic drug |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTX-I | C-terminal cross-linked telopeptide of type I collagen |
| CXCL13 | C-X-C ligand 13 (B cell–attracting chemokine 1) |
| DAS28 | Disease Activity Score in 28 joints |
| DMARD | disease-modifying antirheumatic drug |
| DMC | Data Monitoring Committee |
| EC | Ethics Committee |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| ePRO | electronic patient-reported outcome |
| ESR | erythrocyte sedimentation rate |
| EOT | end of treatment |
| EULAR | European League Against Rheumatism |

| Abbreviation | Definition |
|---|---|
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| F/U | Follow-up |
| GC | glucocorticoid |
| GH | general health |
| GI | gastrointestinal |
| GmTSS | Genant-modified Total Sharp Score |
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HCV Ab | hepatitis C virus antibodies |
| HDL | high-density lipoprotein cholesterol |
| HOMA | Homeostasis Model Assessment |
| hsCRP | high-sensitivity C-reactive protein |
| HPA | hypothalamic-pituitary adrenal |
| IA | intraarticular |
| ICH | International Conference on Harmonisation |
| iDMC | independent Data Monitoring Committee |
| IGRA | Interferon gamma release assay |
| IL | interleukin |
| IV | intravenous(ly) |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (application) |
| IR | insulin resistance |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IxRS | Interactive Response System |
| JAK | janus kinases |
| LDA | low disease activity |
| LDH | lactate dehydrogenase |
| LDL | low-density lipoprotein cholesterol |
| LPLV | last patient, last visit |
| MMP | matrix metalloproteinase |
| MMR | vaccine for measles, mumps, rubella |
| MMRV | vaccine for measles, mumps, rubella, and varicella |
| MTX | methotrexate |
| NCI | National Cancer Institute |

| Abbreviation | Definition |
|---|---|
| ND | not done |
| NE | not evaluated / non-evaluable |
| non-IMP | non-investigational medicinal product |
| NSAID | non-steroidal anti-inflammatory drug |
| OR | odds ratio |
| PD | pharmacodynamic |
| PINP | pro-collagen serum type I N-terminal propeptide |
| pJIA | polyarticular juvenile idiopathic arthritis |
| PK | pharmacokinetic |
| PP | Per Protocol |
| PPI | proton pump inhibitor |
| PRO | patient-reported outcome |
| QW | once per week |
| Q4W | once every 4 weeks |
| RA | rheumatoid arthritis |
| RAID | Rheumatoid Arthritis Impact of Disease (scale) |
| RBC | red blood cell (count) |
| RBR | Research Biosample Repository |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | subcutaneous(ly) |
| SD | standard deviation |
| SDAI | simplified disease activity index |
| sICAM-1 | soluble intercellular adhesion molecule-1 |
| SJC | swollen joint count |
| sJIA | systemic juvenile idiopathic arthritis |
| TB | tuberculosis |
| TCZ | tocilizumab |
| TGF-β | transforming growth factor-ß |
| TJC | tender joint count |
| TNF-α | tumour necrosis factor-α |
| tsDMARD | targeted synthetic disease-modifying antirheumatic drug |
| TST | tuberculin skin test |
| ULN | upper limit of normal |
| US/USA | United States of America |

| Abbreviation | Definition |
|---|---|
| VAS | Visual Analogue Scale |
| WBC | white blood cell (count) |
| WPAI:RA | Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis |

# 1. BACKGROUND

## 1.1 BACKGROUND ON RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by joint pain, swelling, stiffness, and progressive destruction of synovial joints of the hands and feet (Aletaha et al. 2010; Shetty et al. 2014). The incidence is highly variable between nations, but is typically around 40 cases per 100,000 (Symmons 2002). Prevalence estimates in adult populations range from approximately 0.3% to 1.0% (WHO 2003; Gabriel and Michaud, 2009; Montjardino et al. 2011). A study in the United Kingdom found the population minimum prevalence of RA is 1.16% in women and 0.44% in men (Symmons et al. 2002). The reported prevalence of RA in the United States was about 1.5 million adults in 2007 (Myasoedova et al. 2010), and women were affected three times more than men (Jawaheer et al. 2006). Rheumatoid arthritis affects about 1% of adults aged > 35 years and > 2% of adults aged > 60 years (Helmick et al. 2008; Shetty et al. 2014). Given its higher incidence in adults during their peak productivity years, requirement for long term treatment, and the prospect of severe disability and early mortality, RA carries a great economic impact (Aletaha et al. 2010; Simons et al. 2012).

The etiology of RA is thought to be multifactorial and is not fully understood; however, pro-inflammatory cytokines (tumour necrosis factor [TNF]-α, interleukin [IL]-6, IL-1β) are known to play a role in the disease pathogenesis in RA by propagating inflammation and leading to joint destruction (Majithia and Geraci, 2007). IL-6 and the soluble IL-6 receptor are present in serum and synovial fluids and are seen in higher levels in patients with RA (Mihara et al. 2005). Multiple functions in which IL-6 mediates the systemic and articular features of RA make IL-6 blockade an attractive biologic target therapy for the treatment of RA (Kishimoto 2005).

### 1.1.1 Current Treatment Options

The management of RA rests on several principles, including pharmacological treatment and non-pharmacological measures. Drug treatment comprises disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs); with DMARDs being the mainstay of RA treatment, used either as monotherapy or as combination therapy. These agents are characterized by their capacity to interfere with the entire disease process, including to reduce or reverse signs and symptoms, disability, impairment of quality of life, inability to work, and progression of joint damage (Smolen et al. 2007; Smolen et al. 2014). The DMARDs form two major classes. The first class includes the conventional synthetic compounds (csDMARDs) of methotrexate (MTX), sulfasalazine and leflunomide and the targeted synthetic agent (tsDMARD) tofacitinib, which was specifically designed to target janus kinases (JAKs). The second class includes biological agents (bDMARDs), comprised of five available TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the T cell co-stimulation inhibitor, abatacept, the anti-B cell agent, rituximab, the interleukin (IL)-6 receptor (IL-6R)-blocking monoclonal antibody, tocilizumab (TCZ), the IL-1 inhibitor, anakinra, and the biosimilar (bs)-infliximab (Smolen et al. 2014). The

emergence of biological agents targeting the cytokines well-known to play a role in the pathogenesis of RA (TNF-alpha, IL-6, and IL-1β) has greatly improved the treatment of RA over the past decade (Shetty et al. 2014).

### 1.1.2 Treatment Recommendations

The current European League Against Rheumatism (EULAR) guidelines for the management of RA recommend that therapy with DMARDs be started as soon as the diagnosis of RA is made, with the aim of reaching remission or low disease activity (LDA) (Smolen et al. 2014). The initial treatment strategy in active disease includes MTX (or sulfasalazine or leflunomide in cases of MTX contraindications or early intolerance). Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, and then tapered as rapidly as clinically feasible. If there is no improvement by at most 3 months after the start of treatment, or the target has not been reached by 6 months, therapy should be switched to another csDMARD (in the absence of poor prognostic factors), or a combination of csDMARDs, or augmented with a bDMARD (when poor prognostic factors are present), such as TCZ, a TNF inhibitor or abatacept, and, under certain circumstances, rituximab. If a first bDMARD has failed, it is recommended that the patient is treated with another bDMARD. Tofacitinib may be considered after biological treatment has failed, if available. For patients in persistent remission after having tapered glucocorticoids, tapering of bDMARDs can be considered, especially if this treatment is combined with a csDMARD. In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered (Smolen et al. 2014).

## 1.2 GLUCOCORTICOIDS IN THE TREATMENT OF RA

Since their discovery in 1948, glucocorticoids (GCs) have been among the most frequently used anti-inflammatory and immunosuppressive drugs for RA. More than half of patients with RA receive concomitant treatment with low-dose GCs (≤ 7.5 mg/day) more or less continuously, as evidenced by the percentage of RA patients treated with GC at inclusion in phase II–IV trials of biological drugs (Spies et al. 2011; Buttgereit 2012). Over the past three decades, a reduction of mean initial prednisone dose from 10.3 mg/day in 1980–1985 to 3.6 mg/day in 2000–2004, with 86% of patients seen in 2000–2004 having initial doses < 5 mg/day (Pincus et al. 2015).

Glucocorticoids have a well-established efficacy in controlling the disease symptoms and structural progression in RA, and are often used concomitantly with DMARDs (Hoes et al. 2010; Spies et al. 2011; Smolen et al. 2014; Santiago and da Silva, 2015). However, due to the pleiotropic actions of GCs, there is a considerable concern regarding their toxicity, especially at higher doses and longer duration of therapy (Spies et al. 2011). The variety of adverse events (AEs) reported to be associated with GC use comprises diabetes mellitus/glucose intolerance, cardiovascular disease (such as myocardial infarction, hypertension), obesity, osteoporosis, fractures, and infections, among others; refer to Table 1 (Schettler et al. 1999; Curtis et al. 2006; Da Silva et al. 2006; Hoes et al. 2010; Huscher et al. 2009; McDonough et al. 2009; Spies et al. 2011; Strangfeld et al. 2011; Aviña-Zubieta et al. 2013; Duru et al. 2013; Kawai et al. 2013; del Rincón et al. 2014). Of note, the estimation of the risk of developing GC toxicity is challenging, as in

most studies AEs have not been assessed systematically (Hoes et al. 2010; Spies et al. 2011). In addition, there is a considerable overlap between adverse experiences associated with RA itself, and the events considered as side effects of GCs, such as cardiovascular disease, osteoporosis and fractures, and decreased insulin sensitivity (Santiago and de la Silva, 2015).

**Table 1: Summary of Key Adverse Events Associated with GC Use in Patients with RA**

| **Placebo-controlled studies** | |
|---|---|
| **AE** | **Dose range and application** |
| Osteoporosis | chronic medium dose<br>IM |
| Cardiovascular disease (i.e. MI) | chronic medium dose<br>step-down<br>IM |
| Diabetes | chronic medium dose<br>IM |
| Weight gain | IM |
| Renal dysfunction | chronic medium dose<br>step-down |
| Peptic ulcer disease | chronic medium dose |
| Hypertension | chronic medium dose<br>step-down<br>IM |

| **Uncontrolled Studies** | |
|---|---|
| **AE** | **Dose range and application** |
| Osteoporosis | chronic medium dose<br>chronic high<br>step-down |
| Cardiovascular disease (i.e. MI) | chronic medium dose<br>chronic high |
| Diabetes | chronic medium dose<br>chronic high<br>step-down |
| Weight gain | chronic medium dose<br>step-down |
| Renal dysfunction | chronic medium dose<br>step-down |
| Peptic ulcer disease | chronic medium dose<br>step-down |
| Hypertension | chronic medium dose<br>chronic high<br>step-down |

AE: adverse event; IM: intramuscular; MI: myocardial infarction
*Source: Duru et al. 2013*

Results from several recently published systematic reviews and meta-analyses generally support the adequate safety of low-to medium dose GCs, including over long-term. A meta-analysis of low- to medium-dose GCs used for at least 1 month found that the reported GC-related AE rate was 43/100 patient years in RA studies, which was lower compared to other inflammatory diseases (Hoes et al. 2009). A meta-analysis of six

randomized controlled trials (RCTs) with total of 689 patients, investigating the safety of medium to long-term (≥ 2 years) GC therapy in RA found no statistically significant differences between prednisolone (at 5 to 10 mg doses) and placebo in the number of patients withdrawn due to AEs (odds ratio [OR] = 1.09; 95% CI 0.52, 2.25), number of AEs per patient year (OR = 1.19; 95% CI 0.91, 1.57) or the number of serious AEs (OR = 1.06; 95% CI 0.67, 1.67). The efficacy/toxicity ratio for GC therapy was assessed as good (number needed to harm/number needed to treat = 0.25) (Ravindran et al. 2009).

Conversely, a meta-analysis of seven studies found a significant reduction in both lumbar and femoral bone mineral density (BMD) in RA patients receiving low-dose GC (N=353) compared to controls (N=343), suggesting that low-dose GC treatment accelerates bone loss in patients with RA, which overcomes the potential benefit derived from disease control (Lee et al. 2008).

However, a recent review of toxicity data from seven randomized controlled trials concluded, that the toxicity profile of low-dose GCs (up to 10 mg of prednisone equivalent/day for up to 2 years) in RA patients seems mild and hardly different from that described for placebo, except for weight gain and glaucoma. However, the evidence is scarce (limited to 1,100 patient years of exposure) and of poor quality to establish conclusions (Santiago and da Silva, 2015).

Lastly, two dose-related patterns of GC AEs have been observed (Huscher et al. 2009). A linear relationship has been found for the following AEs: cushingoid phenotype, ecchymosis, leg oedema, mycosis, parchment-like skin, shortness of breath and sleep disturbance. Threshold-related AEs comprise: glaucoma, depression/ listlessness and increase in blood pressure (>7.5 mg/day); epistaxis and weight gain (≥ 5 mg/day) and cataract (< 5 mg/day).

The concept that the AEs associated with GC treatment are potentially serious and depend on the dose and duration of use led to recommendations that the minimum dose should be used for the shortest possible time, always in combination with other DMARDs (Smolen et al. 2014; Santiago and de la Silva, 2015). A EULAR task force has developed evidence-based recommendations for the best use and management of GC therapy in all rheumatic diseases (Hoes et al. 2007), and subsequent guidelines focusing on GC use in RA patients (Gorter et al. 2010; Smolen et al. 2014). The EULAR recommendations stipulate that low (≤ 7.5 mg/day) or moderate (7.5 – 30 mg/day) doses of GCs may contribute to a therapeutic benefit if they are given as initial and short duration treatment (Smolen et al. 2010; Smolen et al. 2014). The goal of initial low-dose oral GCs as a bridging add-on therapy on a DMARD background is to achieve low disease activity (DAS28 ≤ 3.2) and to aid reaching remission (DAS28 < 2.6) (GUIPCAR 2007; Smolen et al. 2014; Caporali et al. 2015). The recommended treatment duration is up to 6 months, after which the GC should be tapered as rapidly as clinically feasible. Tapering is seen as either dose reduction or prolongation of intervals between applications (Smolen et al. 2014). The rapid control of disease activity with this regimen (both in terms of clinical and subclinical reduction of the inflammatory process), ensures long-standing structural benefits, which persist even after GC withdrawal (Hoes et al. 2010; Caporali et al. 2015). If the initial regimen is greater than 5 mg/day, dosage tapering to 5 mg/day has recently been recommended as early as is clinically feasible

(possibly after 6 months of treatment), however there are no guidelines specifically addressing this issue; therefore, the decision to taper is made based on clinician expertise and patient preferences (Caporali et al. 2015). There is also limited information concerning GC withdrawal in the context of complex treatment regimens, including both biologic and non-biologic DMARDs (Caporali et al. 2015).

## 1.3 TOCILIZUMAB IN THE TREATMENT OF RA

Tocilizumab (TCZ), is a recombinant humanized anti-IL-6 receptor monoclonal antibody, approved in several countries (in combination with MTX) for the treatment of: (1) severe, active and progressive RA in adults not previously treated with MTX; and (2) moderate to severe RA in adult patients who have not adequately responded to one or more DMARDs or cannot tolerate other approved drug classes for RA. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate (RoActemra SmPC 2015; Al-Shakarchi et al. 2013; Shetty et al. 2014). In addition, TCZ has been approved in some countries for the treatment of systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA), and early RA.

Tocilizumab given intravenously (IV) 8 mg/kg every 4 weeks (Q4W) has obtained first market approval for the treatment of RA in Japan in 2008 (where it is also approved for pJIA, sJIA and Castleman's disease), followed by Europe in 2009, in combination with MTX for the treatment of moderate to severe active RA in adult patients with inadequate response to, or intolerance of, DMARD or TNF antagonist therapy. It may also be administered as monotherapy in the same dose regimen in patients with methotrexate intolerance or with inadequate response to MTX. Since January 2011, in the United States, the indication for treatment with TCZ for RA patients with an inadequate response to one or more TNF antagonists was extended to patients with moderately to severely active RA, and the recommended starting dose is 4 mg/kg Q4W, with an increase to 8 mg/kg based on clinical response (Alten et al. 2010).

The efficacy of TCZ IV as both monotherapy and combination therapy in patients with RA was demonstrated in several advanced phase randomized clinical trials (Al-Shakarchi et al. 2013; Shetty et al. 2014). Of these, there were five pivotal Phase 3 trials and two open-label, long-term treatment extension studies. A brief description of the five pivotal double-blind, randomized, parallel group studies is provided below.

**OPTION** (WA17822): In this study, 623 patients with moderate to severe active rheumatoid arthritis were randomly assigned to receive TCZ 8 mg/kg (n=205), TCZ 4 mg/kg (214), or placebo (204) intravenously every 4 weeks, with methotrexate at stable pre-study doses (10-25 mg/week). The primary endpoint was the proportion of patients with 20% improvement in signs and symptoms of rheumatoid arthritis according to American College of Rheumatology criteria (ACR20 response) at Week 24. The study met its primary endpoint; at 24 weeks, ACR20 responses were seen in significantly more patients receiving TCZ than in those receiving placebo (59% patients in the 8 mg/kg group, 48% in the 4 mg/kg group, 26% in the placebo group; odds ratio [OR] 4.0 [95% CI 2.6-6.1], $p<0.0001$ for 8 mg/kg vs placebo; and 2.6 [1.7-3.9], $p<0.0001$ for 4 mg/kg vs placebo) (Smolen et al. 2008).

**TOWARD** (WA18063): In this study, 1,220 patients with moderate to severe active RA who had an inadequate response to current DMARD therapy, were randomized (2:1 ratio) to treatment with TCZ 8 mg/kg or placebo every 4 weeks for 24 weeks (given in combination with background DMARD therapy). The study met its primary endpoint; at Week 24, the proportion of patients achieving ACR20 was significantly greater in the TCZ plus DMARD group than in the control group (61% versus 25%; p<0.0001) (Genovese et al. 2008).

**RADIATE** (WA18062): This study randomized 499 patients with inadequate clinical response to one or more anti-TNF therapies to receive 8 mg/kg or 4 mg/kg TCZ or placebo (control) intravenously every 4 weeks with stable methotrexate for 24 weeks. The anti-TNF agent was discontinued prior to randomization. The study met its primary endpoint, as ACR20 was achieved at 24 weeks by significantly more patients in the TCZ 8 mg/kg and 4 mg/kg groups compared to control (50.0%, 30.4% and 10.1% of patients, respectively; p<0.001 for both TCZ groups versus control). Patients responded regardless of most recently failed anti-TNF or the number of failed treatments. DAS28 remission (DAS28 < 2.6) rates at Week 24 were clearly dose related, being achieved by 30.1%, 7.6% and 1.6% of 8 mg/kg, 4 mg/kg and control groups, respectively (p<0.001 for 8 mg/kg and p=0.053 for 4 mg/kg versus control) (Emery et al. 2008).

**AMBITION** (WA17824): This study compared TCZ monotherapy (8 mg/kg every 4 weeks) with MTX monotherapy (starting at 7.5 mg/week and titrated to 20 mg/week within 8 weeks) in 673 patients with active RA for whom previous treatment with MTX/biological agents had not failed. To enable sensitivity testing for the non-inferiority claim, the study also included a 3-arm, 8-week sub study that included a placebo arm. The study met its primary endpoint by demonstrating that TCZ compared to MTX treatment was associated with a higher ACR20 response (69.9% vs 52.5%; p<0.001) atWeek24. Similarly, DAS28 < 2.6 rate was significantly higher with TCZ versus control (33.6 vs 12.1%, respectively) at Week 24 (Jones et al. 2010).

**LITHE** (WA17823): In this 2-year study, 1,196 patients with moderate to severe active RA who had an inadequate response to MTX were randomized to treatment with TCZ (8 mg/kg or 4 mg/kg) or placebo every 4 weeks plus MTX. The study met its endpoints of reduction in signs and symptoms, prevention of joint damage and physical function. At 52 weeks, mean change in the total Genant-modified Total Sharp Score (GmTSS) was 0.29 and 0.34 with TCZ 8 mg/kg plus MTX and 4 mg/kg plus MTX, respectively, versus 1.13 with placebo plus MTX (p<0.0001 for both comparisons). Proportions of patients with ACR20, ACR50, and ACR70 improvement and with DAS28 remission were higher in those receiving 8 mg/kg TCZ than in those receiving placebo (p<0.0001 for all comparisons) (Kremer et al. 2011). During Year 2, patients continued the initial double-blind treatment or switched to open-label 8 mg/kg TCZ-MTX. Co-primary endpoints at Week 104 were mean change from baseline in GmTSS and adjusted mean area under the curve (AUC) for change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI). At Week 104, mean change from baseline in GmTSS was significantly lower for patients initially randomized to TCZ-MTX 4 mg/kg (0.58; p=0.0025) or 8 mg/kg (0.37; p<0.0001) than for patients initially randomized to placebo-MTX (1.96). Adjusted mean AUC of change from baseline in HAQ-DI was also significantly lower in

patients initially randomized to TCZ-MTX 4 mg/kg (-287.5; p<0.0001) or 8 mg/kg (-320.8; p<0.0001) than in patients initially randomized to placebo-MTX (-139.4). Signs and symptoms of RA were maintained or showed improvement (Fleischman et al. 2013).

Treatment with TCZ IV was generally well tolerated in the above described clinical studies. Adverse events experienced during treatment with TCZ IV were usually mild to moderate in severity and no increase in the risk of serious adverse events (SAEs) was detected compared to controls. Precautions during treatment with TCZ are related to elevated liver enzymes, elevated low-density lipoprotein, infections, and gastrointestinal perforations (Al-Shakarchi et al. 2013; Shetty et al. 2014).

For further details on these studies, refer to the Investigator's Brochure for TCZ, and for additional key randomized controlled efficacy studies of TCZ IV in patients with RA, refer to the respective publications (Nishimoto et al. 2004; Maini et al. 2006; Nishimoto et al. 2007; Nishimoto et al. 2009a; Yazici et al. 2013; Dougados et al. 2013; Gabay et al. 2013; Weinblatt et al. 2013).

Recently, SC administration of TCZ was approved by the Food and Drug Administration (FDA) for use in the US in patients with RA at a starting dose of 162 mg every other week in patients who weigh < 100 kg, with an increase in frequency to 162 mg every week based on clinical response. In patients who weigh ≥ 100 kg, the starting dose is 162 mg every week. TCZ SC every other week is also approved in Japan, and in the European Union, a starting dose of TCZ-SC every week is approved, with modification to every other week for the management of laboratory abnormalities (Kivitz et al. 2014).

Two Phase 3 double-blind, randomized controlled trials demonstrated the efficacy and safety of the SC formulation of TCZ in patients with RA, and are briefly described below.

**SUMMACTA** (WA22762): This randomized, double-blind, parallel group study compared the efficacy and safety of SC versus IV administration of TCZ in patients with moderate to severe active RA with an inadequate response to DMARDs. A total of 1,262 patients were randomized to receive TCZ 162 mg SC weekly (plus IV placebo every 4 weeks), or TCZ 8 mg/kg IV every 4 weeks (plus SC placebo weekly) for 24 weeks. The double-blind period was followed by a 72-week open-label treatment with some switching of SC and IV administration (without placebo). Patients continued on their stable dose of DMARDs throughout the study. The study showed that TCZ 162 mg SC weekly was non-inferior to TCZ 8 mg/kg IV every 4 weeks, when both are combined with DMARDs. At Week 24, 69.4% of TCZ SC-treated patients versus 73.4% of TCZ IV-treated patients achieved an ACR20 response (primary endpoint; weighted difference between groups -4.0%, 95% CI -9.2 to 1.2); hence the 12% non-inferiority margin was met. ACR50/70 responses, DAS28 and physical function improvements were comparable between the TCZ SC and TCZ IV groups. The safety profiles of TCZ SC and TCZ IV were similar, and the most common AE was infection. Injection-site reactions occurred more frequently in the TCZ SC group than in the TCZ IV group. No anaphylaxis was reported over the 24 weeks (Burmester et al. 2014).

To further characterize the efficacy and safety of a lower dose of TCZ SC, the BREVACTA study compared TCZ SC 162 mg every other week with SC administration

of placebo every other week in adult patients with moderate to severe RA who had an inadequate response to ≥ 1 DMARDs.

**BREVACTA** (NA25220): In this two-arm, randomized, double-blind, placebo-controlled, parallel-group study, 656 patients received 162 mg TCZ SC every other week, or a matching placebo regimen until Week 24 and 162 mg TCZ SC open-label from Week 24 to Week 96. Data to Week 24, including the primary end point, are currently available. TCZ SC was superior to placebo for ACR20 response (primary endpoint) at Week 24 (60.9% versus 31.5%; P < 0.0001). All secondary end points showed TCZ SC to be superior to placebo, including ACR50 (40% vs 12%, respectively; P < 0.0001), ACR70 response (20% vs 5%, respectively; P < 0.0001) and DAS28 remission (DAS28 < 2.6; 32% versus 4%; P < 0.0001). TCZ SC was well tolerated and its safety profile was comparable with that of previous intravenous TCZ studies. Adverse events and SAEs were comparable between the TCZ SC and placebo groups; 4.6% and 3.7% of patients had at least one SAE, respectively, and infection was the most common SAE in 2.1% and 1.8% of patients, respectively. There were 3 deaths in the TCZ SC group and none in the placebo group. More injection site reactions occurred with TCZ SC than placebo (7.1% versus 4.1%). No anaphylaxis or serious hypersensitivity reactions occurred (Kivitz et al. 2014).

There is also evidence of sustained long-term efficacy and a generally good safety profile of TCZ from extension studies. In an open-label, long-term extension of a Phase II multi-centre, double-blind, placebo-controlled trial, that enrolled 163 patients with refractory RA (Nishimoto et al. 2004), following an initial 3-month treatment, 143 patients continued to receive TCZ IV monotherapy (8 mg/kg) every 4 weeks. Concomitant therapy with NSAIDs and/or oral prednisolone (10 mg daily maximum) was permitted. Of the 143 patients, 94 (66%) had completed 5 years of follow-up. At 5 years, 79 (84%), 65 (69%) and 41 (44%) of the patients achieved ACR20, ACR50, and ACR70 improvement, respectively. Remission defined as DAS28 less than 2.6 was achieved in 52 (55%) of the patients. Of the 88 patients receiving GCs at baseline, 78 (89%) were able to decrease their GC dose and 28 (32%) discontinued GCs (Nishimoto et al. 2009b).

Additional evidence of a GC-sparing effect of TCZ is available from a recently published open label, observational, retrospective multi-centre study that evaluated the impact of TCZ treatment in 130 RA patients treated with oral GCs for > 3 months. The mean ± standard deviation (SD) baseline dose of GCs was 10.0 ± 8.2 mg/day prednisone equivalent (91.5, 51.5, 20.0 and 9.2% of patients received a daily dose of 5, 10, 15 and 20 mg, respectively). During the study period there was a significant early GC-sparing effect. The mean daily dose of oral GCs fell from 10.0 mg at baseline to 8.7 mg at Week 4, 8.0 mg at Week 8, 7.5 mg at Week 12, and 6.5 mg at Week 24 (p<0.0001). In parallel, among the 90 patients not receiving GCs at baseline, 13 received GCs during the study period. When these patients were included in the analysis, the mean daily dose of oral GCs fell from 9.1 mg at baseline to 8.2 mg at Week 4, 7.9 mg at Week 8, 7.5 mg at Week 12, and 6.4 mg at Week 24 (p<0.0001). 11.5% of the patients were able to stop GCs after 24 weeks. The mean DAS28 fell from 5.1 ± 1.4 at baseline to 3.0 ± 1.4 at Week 24 (p<0.0001) (Fortunet et al. 2014). The relevance of this rapid and long-lasting GC-sparing effect is underscored by findings of a post-marketing study involving nearly

4,000 patients, in which GC therapy with ≥ 5 mg/day prednisone equivalent was associated with severe infections during the first 24 weeks of TCZ (Koike et al. 2011), and earlier observations of gastrointestinal perforations in RA patients receiving GCs (Fortunet et al. 2014).

## 1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Clinical recommendations for the management of systemic GC therapy in RA state that a reduction and even a discontinuation should be attempted once remission or LDA has been reached; however, a GC reduction schedule has not yet been standardized. There are no formal recommendations on when and how to taper initial GC regimens from doses ≥ 5 mg/day; therefore, the decisions to taper are made based on clinician expertise and patient preferences (Caporali et al. 2015). There is also limited information concerning GC withdrawal in the context of complex treatment regimens, which include both biologic and non-biologic DMARDs (Caporali et al. 2015). In addition, complete discontinuation of GCs is often hampered by steroid withdrawal symptoms or the fear thereof.

As detailed in Section 1.3, the efficacy and safety of TCZ in combination with MTX in the treatment of RA patients refractory to synthetic DMARDs or/and anti-TNF is well established. Tocilizumab can also be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. However, it has not been systematically investigated in a randomized double-blind study whether treatment with TCZ in patients receiving a moderate or low dose GC could also enable reduction or discontinuation of the GC while maintaining disease symptom control. Several observational studies provided preliminary evidence that this might be achievable. Data from Japanese studies of TCZ monotherapy (N=601) showed that of the 546 patients taking GCs at baseline, 77.8% were able to decrease their GC dose during the study period, while 35.2% discontinued GCs altogether (Nishimoto et al. 2010). A significant early GC-sparing effect was also reported in the above described retrospective observational study evaluating TCZ in 130 RA patients treated with oral GCs for > 3 months. The study showed a significant, persistent decline in GC dose from 9.1 mg at baseline to 6.4 mg at Week 24 ($p<0.0001$), and complete discontinuation of GCs in 11.5% of the patients (Fortunet et al. 2014). In a 12-months retrospective observational SPARE-1 study (N=307), the percentage of patients receiving prednisone at >10 mg/day and between 7.5 and 10 mg/day was reduced from 30% to 14%, and from 44% to 14%, respectively, and 20% of patients discontinued GCs altogether (Saraux et al. 2013). Further supportive evidence comes from the open-label ACT-ALONE study (ML25252) that aimed to determine the proportion of RA patients with LDA able to discontinue oral GC within 20 weeks, with confirmation of the GC-free status and maintained LDA 4 weeks later. LDA was achieved with standard treatment including oral GC and TCZ (8mg/kg IV perfusion Q4W), with or without DMARD in a 6-month observation phase, and was followed by a 28-week interventional phase, consisting of oral methylprednisolone according to a fixed dose reduction schedule over 20 weeks, and TCZ, with or without DMARDs. Of the 43 patients analysed, 58.1% discontinued GC within 20 weeks with confirmation of LDA 4 weeks later, and 93.3% were able to reduce GC by ≥50% after 24 weeks, with disease activity and levels of pain and disability

remaining at a low level throughout the interventional phase of the study (Ribbens et al. 2014). The GC-sparing effect of TCZ was also noted in the interim analysis (N=589) of the ongoing, prospective 2-year non-interventional ICHIBAN study. During the observation period, the mean daily GC dose decreased continuously from 9.4 at baseline to 5.3 mg/day at Week 104. Of the patients receiving GCs at baseline, 19.2% could discontinue GC treatment, 52.7% could reduce the dose, and a dose increase was necessary in only 10.0% of the patients. The proportion of patients not needing concomitant GC increased by 11.4% to 29.0% during observation and the proportion of daily GC dose ≤ 5 mg increased from 59.7% to 76.5% (Specker et al. 2014).

A central feature of RA is an imbalance of cytokine production, with a relative excess of pro-inflammatory molecules, including IL-1, IL-6, IL-17, IL-18, and TNF-α, compared with anti-inflammatory mediators such as IL-10 or transforming growth factor-ß (TGF-ß) (de Paz et al. 2010). Glucocorticoids are potent inhibitors of inflammation, and this is at least partly due to their ability to inhibit the synthesis of pro-inflammatory cytokines (such as IL-1, IL-6, and TNF-α). In non-clinical models, adrenalectomy or GC antagonists were shown to potentiate TNF, IL-1 and IL-6 production (Fantuzzi and Ghezzi, 1993). In humans, plasma levels of IL-6 have been reported to decrease during prednisone treatment (Buttgereit et al. 2010). In addition, a genetic polymorphism characterized by high IL-10/low TNF-α expression has been found to be a predictor of response to GC therapy (de Paz et al. 2010). The mechanism of anti-inflammatory action of GCs also includes the apoptosis in mature T cells and an effect on the differentiation of T-cells. As such, there appears to be some redundancy in the anti-inflammatory effects of GCs and those of the humanized anti-IL 6 receptor antibody TCZ. Hence it is possible, that GCs do not contribute to the level of disease control achieved with TCZ to the same extent as observed during their co-administration with TNF inhibitors.

Therefore the rationale for this study is to assess the potential GC-sparing effect of TCZ, and its ability to enable discontinuation of GCs. In addition, the study will explore potential factors associated with successful discontinuation of GCs. To eliminate potential patient and physician bias, GC treatment will be tapered and discontinued in a double-blind manner, starting from a dose-level of 5 mg/day prednisone. At this dose level and below, GCs might not significantly contribute to disease control in patients who reached LDA state during treatment with TCZ.

Furthermore, the goal of the study is to ultimately inform therapeutic regimens with TCZ which do not require low-dose steroids while keeping the level of disease control, thereby improve on the benefit risk ratio for patients and as such, a steroid reduction or elimination would be considered as a clear patient benefit. The potential risks of steroid withdrawal are managed by two strategies in this trial. First, a rescue medication scheme will be available to manage potential loss of efficacy in patients which taper steroids. Second, education and guidance about detection and management of potential steroid withdrawal syndrome will mitigate this rare but potential side-effect. In summary, the overall benefit risk assessment for patients participating in this trial is considered positive.

# 2. OBJECTIVES

## 2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To compare the impact on disease activity of continued vs. tapered prednisone in RA patients with stable LDA (DAS28 ESR score ≤ 3.2), as assessed by the change in DAS28 ESR between randomization and Week 24 post-randomization.

The key secondary efficacy objective for this study is as follows:

- To compare the proportion of patients who continue vs. taper prednisone with LDA (DAS28 ESR score ≤ 3.2) at Week 24 post-randomization, who have not suffered a flare due to RA and who showed no confirmed adrenal insufficiency requiring replacement therapy.

Other secondary efficacy objectives for this study are as follows:

- To compare, between patients who continue vs. taper prednisone:
  - changes in disease activity measures, such as clinical disease activity index (CDAI) and simplified disease activity index (SDAI) from randomization to Week 24 post-randomization
  - the proportion of patients with ≥ 1 RA flare, the time to first RA flare and the number of RA flares
  - the proportion of patients with ≥ 1 administration of RA flare rescue medication, the time to first administration, and the number of administrations of RA flare rescue medication
  - cumulative prednisone exposure (dose) between randomization and Week 24 post-randomization
  - the proportion of patients who maintain LDA (DAS28 ESR score ≤ 3.2) and the proportion of patients who maintain the baseline disease activity level at Week 24 post-randomization
  - the proportion of patients who permanently discontinue study treatment due to insufficient RA flare control
  - changes in the ACR core set from randomization to post-randomization Week 24
  - to identify predictors of successful prednisone dose-tapering at Week 24 post-randomization. Variables that may be assessed include, but may not be limited to: age, gender, smoking status, body weight, duration of prior prednisone treatment, prior bDMARD therapy, use of csDMARDs at randomization, bone remodelling.

## 2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of TCZ during the randomized phase of the study, based on an assessment of adverse events (AEs), vital signs, physical examination and clinical laboratory tests, including immunogenicity, in patients with rheumatoid arthritis who continue vs taper prednisone
- To describe the safety of the proposed prednisone-tapering scheme.

## 2.3 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO)-related objectives for this study include the following:

- To compare changes in PROs between patients with rheumatoid arthritis who continue vs taper prednisone, as measured by the:
  - Rheumatoid Arthritis Impact of Disease (RAID)
  - Health Assessment Questionnaire - Disability Index (HAQ-DI)
  - Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA).

## 2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore variables pointing to a potential benefit of prednisone tapering (such as bone remodelling) in patients who continue vs taper prednisone.
- To assess non-inherited biomarkers associated with RA biology and TCZ biology in patients who continue vs taper prednisone.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

This is a Phase IIIb/IV, two-arm, randomized, double-blind, placebo-controlled, parallel-group, international, multicentre trial. The primary study objective is to compare the change in disease activity (as assessed by DAS28 ESR) from randomization to Week 24 post-randomization, in patients with stable LDA (DAS28 ESR score ≤ 3.2) who have been randomized to either continue or taper prednisone in a double-blinded fashion. Patients can enter and be randomized into this study via two tracks. In order to reach the randomization target of 226 patients, between 240 and 450 patients are planned to be recruited via both tracks in parallel over an approximately 1-year period. Given that the randomization ratio will differ between the two tracks, recruitment of patients into the two tracks will be steered to achieve the randomization target without exceeding the total number of 450 recruited patients. A Steering Committee will oversee the general conduct of the study. An independent Data Monitoring Committee (iDMC) will share responsibility for evaluating the safety of the patients participating in the trial at regular intervals throughout the study.

*Track TCZ-experienced patients*

This track consists of patients who received TCZ for at least 24 weeks prior to randomization, either SC, at a dose of 162 mg once a week (QW), or IV, at a dose of 8 mg/kg every 4 weeks (Q4W), not exceeding 800 mg/dose.

Furthermore, eligible patients must have received 5 – 15 mg/day oral prednisone (or GC equivalent) for at least 20 weeks prior to the Screening Visit, although they must be on 5 mg/day oral prednisone or GC equivalent at the Screening Visit. Eligible patients must have a DAS28 ESR score ≤ 3.2 at the Screening Visit. (Eligibility criteria: see Section 4.1.2 and Section 4.1.3).

The TCZ-experienced Screening Visit occurs up to 6 weeks prior to randomization.

TCZ-experienced patients will be switched to Sponsor provided open-label prednisone 5 mg/day after signed informed consent, and as per Section 4.3.2.2.

Patients on csDMARD therapy at the Screening Visit should be maintained on this therapy until the end of the study, and no new csDMARD may be initiated after the patient has signed the informed consent. Modification of stable csDMARD therapy is restricted, as per Section 4.4.1.1.

Oral and other systemic GCs not provided by the Sponsor are forbidden after signed informed consent. Intra-articular or parenteral GCs are forbidden within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone). See Section 4.3.2.2 for specific instructions.

During the Screening Period, other analgesics and anti-inflammatory drugs (e.g. NSAIDs, acetaminophen) are allowed. If clinically feasible and safe, investigators should encourage patients to withhold these drugs for 12-24 hours prior to the randomization visit at which the baseline efficacy assessment is conducted. See Section 4.4.1.2 for specific instructions.

Patients will be randomized and enrolled in the study if they meet the randomization criteria (see Section 4.5.10):

a) Fulfils all inclusion and none of the exclusion criteria;

b) Screening Visit occurred up to 6 weeks prior to randomization;

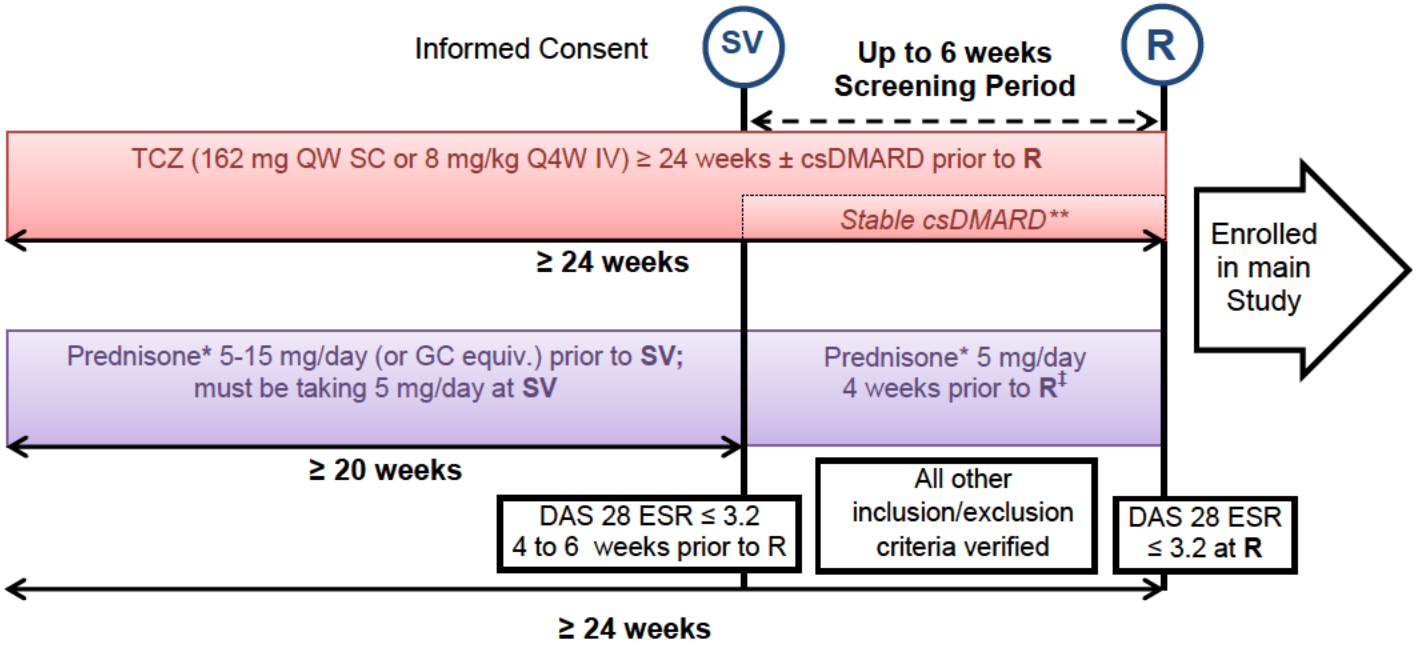
c) DAS28 ESR score ≤ 3.2 at randomization;

d) Receiving prednisone 5 mg/day, and no other oral GC, at randomization and for ≥ 4 weeks prior to randomization;

e) Received no intra-articular or parenteral GCs within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone).

See Figure 2 for a graphical representation of the study design emphasizing the pre-randomization period for *Track TCZ-experienced* patients.

**Figure 2: Track TCZ-experienced patients (pre-randomization)**




**SV: Initial Screening Visit (occurs up to 6 weeks prior to R)**
**R: Randomization Visit**

* Oral

‡ Patient will be switched to sponsor-provided open label (OL) Prednisone at the screening visit. Please refer to Section 4.3.2.2 for special instructions regarding switching to OL Prednisone

** csDMARD dose increase or initiation of new csDMARDs is prohibited during the 4 weeks prior to randomization. Dose reductions or discontinuation is allowed for safety reasons.

DAS: Disease Activity Score; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; equiv: equivalent; ESR: erythrocyte sedimentation rate; GC: glucocorticoid; IV: intravenous(ly); QW: once every week; Q4W: once every 4 weeks; SC: subcutaneous(ly); TCZ: tocilizumab

*Track TCZ-naïve patients*

This track consists of patients who have not received any prior treatment with TCZ, or whose previous TCZ treatment occurred > 12 months prior to screening, and TCZ was not discontinued due to lack of efficacy, side effects, or any other safety concerns.

At the Screening Visit, eligible patients must have active RA defined by DAS28 ESR > 3.2, must be considered by the investigator as inadequate responders to csDMARDs or bDMARDs, and must be receiving oral prednisone 5 to 15 mg/day (or GC equivalent).

Patients fulfilling all eligibility criteria will be enrolled in the 24-week Lead-in Phase, during which time they will receive open-label TCZ SC at a dose of 162 mg QW or open-label TCZ IV at a dose of 8 mg/kg Q4W, not exceeding 800 mg/dose. The choice between TCZ SC or TCZ IV will be made by the investigator, depending on the local availability and individual patient acceptance and tolerability of the SC formulation.

During the Lead-in Phase, the dose of prednisone (or GC equivalent) will be tapered down to prednisone 5 mg/day (if clinically feasible) according to a scheme determined by the investigator.

**All patients who are not on prednisone 5 mg/day (or GC equivalent) at the Lead-in Week 20 Visit will be withdrawn from the study.**

Patients who are on prednisone 5 mg/day (or GC equivalent) at the Lead-in Week 20 Visit will be treated the following way:

- **Patients with a DAS28 ESR ≤ 3.2** at the Lead-in Week 20 Visit will be switched to Sponsor-provided open-label prednisone 5 mg/day for an additional 4 weeks. Patients on csDMARD therapy at the Lead-in Week 20 Visit should be maintained on this therapy until the end of the study, and no new csDMARD may be initiated after this visit. Modification of stable csDMARD therapy is restricted, as per Section 4.4.1.1.
- **Patients with a DAS28 ESR > 3.2** at the Lead-in Week 20 Visit will be withdrawn from the study, unless they have improved considerably: DAS28 ESR score < 4.4 and a change in DAS28 ESR score ≥ 1.2 compared to baseline. **Considerably improved patients** at Lead in Week 20 (DAS28 ESR score > 3.2 and < 4.4 and a change in DAS28 ESR score ≥ 1.2 compared to baseline) may continue TCZ SC and prednisone 5 mg/day (or GC equivalent) treatment for an additional 4 weeks. At the Lead-in Week 24 Visit, patients will be switched to Sponsor provided open-label prednisone 5 mg/day for an additional 4 weeks if:

  1. on prednisone 5 mg/day (or GC equivalent), and
  2. DAS28 ESR ≤ 3.2 (patients not meeting these criteria will be withdrawn).

  Patients on csDMARD therapy at the Lead-in Week 24 Visit should be maintained on this therapy until the end of the study, and no new csDMARD may be initiated after this visit. Modification of stable csDMARD therapy is restricted, as per Section 4.4.1.1.

Oral and other systemic glucocorticoids not provided by the Sponsor are forbidden during the 4 weeks prior to randomization, but otherwise permitted during the Lead-in Phase. Intra-articular or parenteral glucocorticoids are forbidden within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone). See Section 4.3.2.2 for specific instructions.

During the Lead-in Phase, other analgesics and anti-inflammatory drugs (e.g. NSAIDs, acetaminophen) are allowed. If clinically feasible and safe, investigators should encourage patients to withhold these drugs for 12-24 hours prior to visits at which efficacy assessments are conducted. See Section 4.4.1.2 for specific instructions.

RA flares are treated according to standard clinical practice during the Screening and Lead-in Phase.

*Track TCZ-naïve* patients will be randomized if they meet the following randomization criteria (as per Section 4.5.10):

a) DAS28 ESR score ≤ 3.2 at most recent scheduled Lead-in Visit 4 weeks prior to randomization;

b) DAS28 ESR score ≤ 3.2 at randomization;

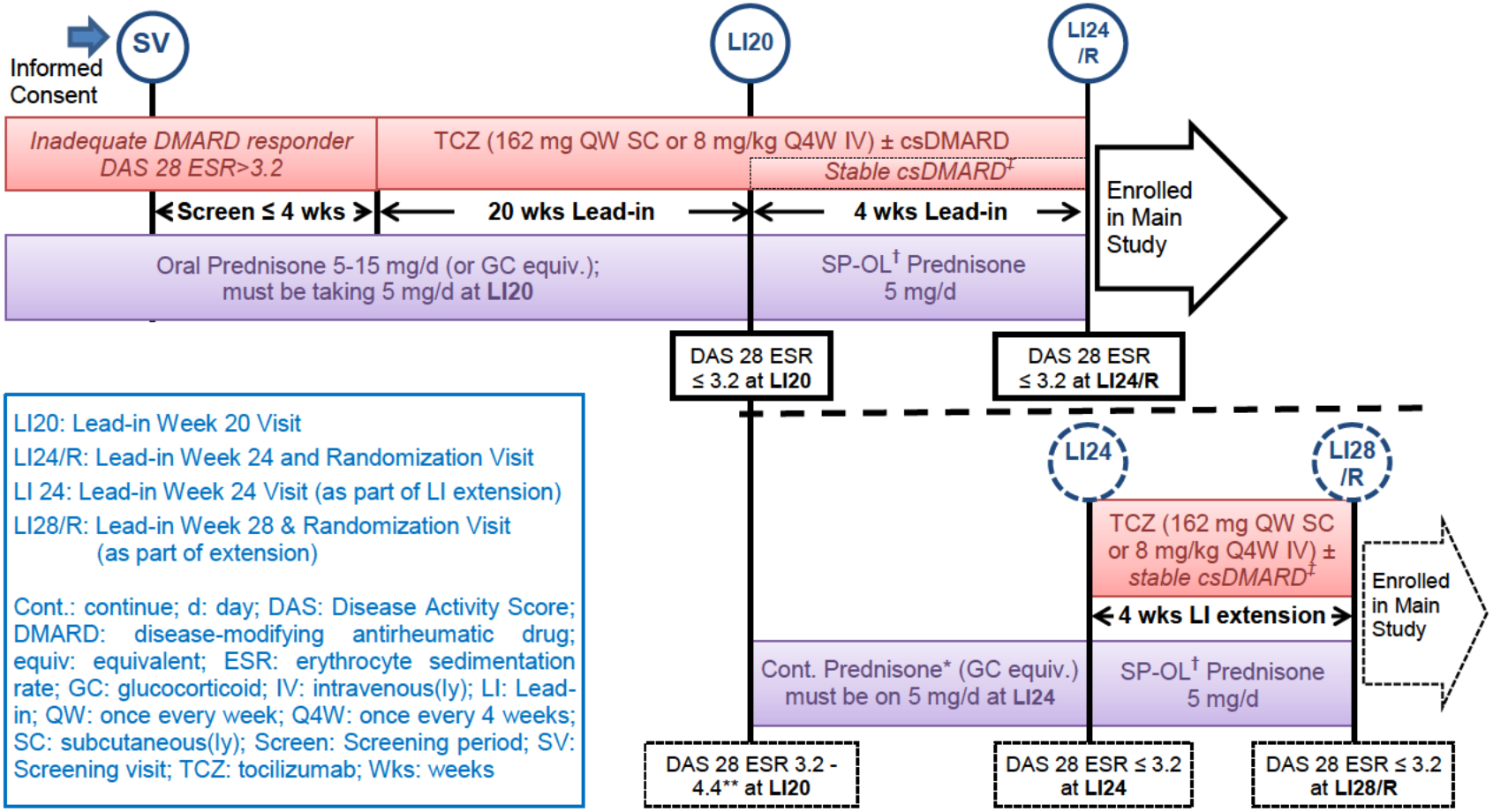
c) Receiving prednisone 5 mg/day, and no other oral GC, at randomization and for ≥ 4 weeks prior to randomization;

d) Received no intra-articular or parenteral GCs within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone).

Patients who are withdrawn during the Lead-in Phase will attend a Study Treatment Discontinuation Visit, followed in 4 weeks by a Safety Monitoring Visit (see Appendix 3). These patients will be subsequently treated outside of the study according to local clinical practice at the discretion of the investigator.

See Figure 3 for a graphical representation of the study design emphasizing the pre-randomization period (including the Lead-in Phase) for *Track TCZ-naïve* patients.

**Figure 3: Track TCZ-naïve patients (pre-randomization)**




LI20: Lead-in Week 20 Visit
LI24/R: Lead-in Week 24 and Randomization Visit
LI 24: Lead-in Week 24 Visit (as part of LI extension)
LI28/R: Lead-in Week 28 & Randomization Visit (as part of extension)

Cont.: continue; d: day; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; equiv: equivalent; ESR: erythrocyte sedimentation rate; GC: glucocorticoid; IV: intravenous(ly); LI: Lead-in; QW: once every week; Q4W: once every 4 weeks; SC: subcutaneous(ly); Screen: Screening period; SV: Screening visit; TCZ: tocilizumab; Wks: weeks

* Oral

† SP-OL Prednisone: Sponsor provided open-label prednisone (oral)

** The Lead-in Phase may be extended 4 weeks at LI20 for patients on 5 mg/day prednisone (or GC equiv.) and with DAS28 ESR >3.2 and < 4.4 and a change in DAS28 ESR score ≥ 1.2 compared to baseline.

‡ csDMARD dose increase or initiation of new csDMARDs is prohibited after LI20 (or extension LI24 for patients receiving a 4 week extension). Dose reductions or discontinuation is allowed for safety reasons.

*Randomization*

Patients are eligible to be randomized for the study if they meet the randomization criteria (see Section 4.5.10).

Randomization numbers will be generated by Roche or its designee and provided to the Interactive Response System (IxRS). Prior to entering the 24-week double-blind Tapering Phase, patients will be randomly assigned (1:1) to one of two treatment groups, either continuing 5 mg/day of prednisone or tapering prednisone in a double-blinded fashion. It is predicted that approximately 95% of patients entering from *Track TCZ-experienced patients* and 50% of patients entering from *Track TCZ-naïve patients* will be randomized, resulting in approximately 226 randomized patients in total.

*Track TCZ-naïve* patients who do not meet the randomization criteria will attend a Study Treatment Discontinuation Visit, followed 4 weeks later by a Safety Monitoring Visit (see Appendix 3). These patients will be subsequently treated outside of the study according to local clinical practice at the discretion of the investigator.

*24-week Double-blind Tapering Phase*

During the 24-week Tapering Phase, randomized patients will receive double-blinded treatment with either:

- Blinded study prednisone 5 mg/day, or
- Blinded study tapering regimen consisting of 1 mg decrements of study prednisone every 4 weeks. Study prednisone will be replaced with increasing amounts of placebo during the tapering.

All randomized patients will be treated with open-label TCZ SC (162 mg QW) or TCZ IV (8 mg/kg Q4W, not exceeding 800 mg/dose). Initiation of new csDMARD is forbidden for all patients. Patients must have their existing csDMARD therapy maintained stable throughout the Tapering phase (see Section 4.4.1.1 for specific instructions):

- csDMARD dose may not be increased,
- csDMARD dose reductions or discontinuation is allowed for safety reasons.

The use of systemic glucocorticoids which are not provided by the Sponsor are generally prohibited during the Tapering Phase, with the exception of treating or preventing serious illness, particularly serious infections or adrenal insufficiency or crisis (see Section 4.3.2.2 for specific instructions).

Other analgesics and anti-inflammatory drugs (e.g. NSAIDs, acetaminophen) are allowed. If clinically feasible and safe, investigators should encourage patients to withhold these drugs for 12-24 hours prior to visits at which efficacy assessments are conducted (see Section 4.4.1.2 for specific instructions).

Patients who successfully complete the Tapering Phase will attend a Study Treatment Discontinuation visit at Week 24, and a Safety Follow-up Visit at Week 28 (see Appendix 2).

Patients who are prematurely withdrawn from treatment during the 24-week Tapering Phase will attend a Study Treatment Discontinuation Visit, followed in 4 weeks by a Safety Monitoring Visit. These patients will be treated thereafter according to the investigator's discretion and encouraged to attend the Week 24 Limited Assessment Visit (see Appendix 3).

Patients who prematurely discontinue study medication will not be replaced.

*RA Flare Assessment and Treatment during the 24-week Double-blind Tapering Phase*

**RA flare assessment and treatment must be conducted according to the instructions in Section 4.5.11.**

During the 24-week Tapering Phase, an RA flare may be detected at any scheduled or unscheduled visit, and is defined as:

- a current DAS28 ESR score > 3.2, and
- an increase in DAS28 ESR score > 0.6 from the randomization visit value.

For a patient experiencing an RA flare, TCZ and study prednisone will continue to be dispensed as planned and the blind maintained. The patient will also receive a 2-week course of RA flare rescue medication, consisting of 5 mg/day of Sponsor provided open-label prednisone. Dose increases to existing csDMARDs or addition of new csDMARDs or any other RA therapy is prohibited (as per Sections 4.4.1 and 4.4.2).

Patients will need to be followed up with a Flare Assessment at the end of this 2-week course. Patients will be determined to have either a resolved RA flare or a second RA flare, **according to criteria defined in Section 4.5.11**. Patients will be withdrawn from the study treatment and followed up and treated as per Appendix 3 if RA flares do not resolve after treatment of the second RA flare.

*Safety Follow-up Phase*

Patients completing the 24-week Tapering Phase will undergo a Safety Follow-up Visit. This visit will occur 4 weeks after the completion of the Tapering Phase (i.e. at Week 28 post-randomization).

*Post-study Treatment*

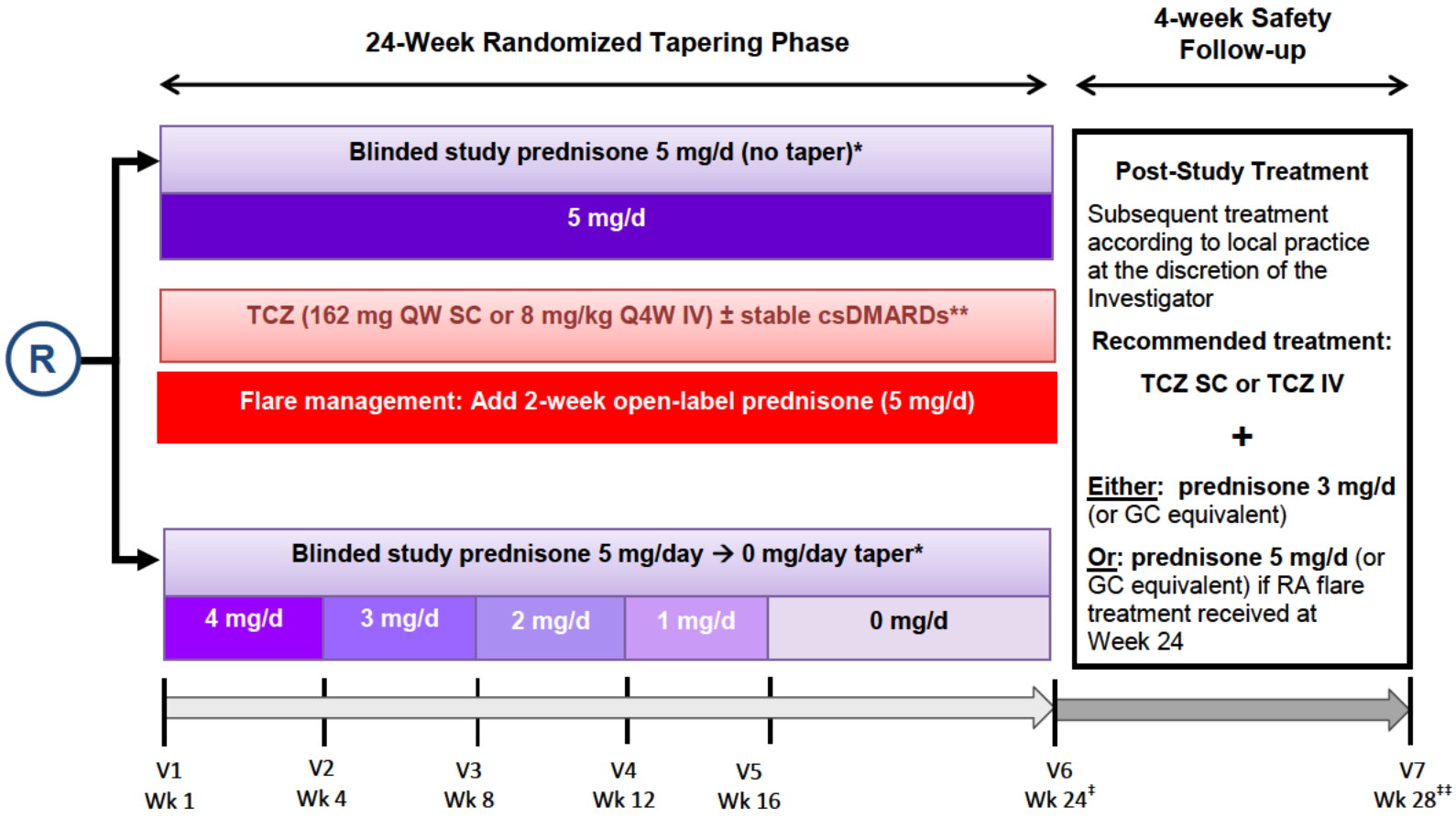
Management of patients completing the 24-week Tapering Phase, including treatment of any potential RA flares following completion of study treatment, will be according to local standard clinical practice at the discretion of the investigator. However to ensure the scientific integrity of the study and to maintain the blind until database lock, it is recommended that patients completing the 24-week Tapering Phase be treated with open-label 3 mg/day of prednisone and continue TCZ (SC or IV). Higher doses of prednisone, e.g. 5 mg/day may be required in patients who were receiving RA flare rescue medication at Week 24 post-randomization.

The end of the trial is defined as the date of the last visit of the last participating patient in this study. Study unblinding will occur after data base lock, and patients will be subsequently informed as to their previously assigned treatment groups.

A Schedule of Assessments is provided in Appendix 1, Appendix 2 and Appendix 3.

See Figure 4 for a graphical representation of the study design emphasizing the post-randomization period applicable to all randomized patients from both tracks.

**Figure 4: All patients: Randomized Tapering Phase, Post-Study Treatment, and Safety Follow-up**




* Oral prednisone ± placebo
** csDMARD dose increase or initiation of new csDMARDs is prohibited. Dose reductions or discontinuation is allowed for safety reasons.
‡ Final assessment visit
‡‡ End of Study Visit / Safety Monitoring Visit
d: day; DMARD: disease-modifying anti-rheumatic drug; OL: open label; QW: once per week; RA: rheumatoid arthritis; SC: subcutaneous(ly); TCZ: tocilizumab
R = 1:1 randomization of patients from both tracks (*TCZ-experienced* and *TCZ-naïve*)

### 3.1.1 Steering Committee

The Steering Committee composed of Sponsor and external clinical representatives, will oversee the scientific validity and general conduct of the study as well as dissemination of the study results. Further details regarding the roles and responsibilities of the Steering Committee and its members are provided in the Steering Committee Charter.

### 3.1.2 Independent Data Monitoring Committee

An iDMC will share responsibility for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. Efficacy data will only be provided if required by the iDMC to estimate risk-benefit for patients.

The schedule of iDMC review will be determined by the iDMC and described in the iDMC Charter. Further details regarding the roles and responsibilities of the iDMC are provided in the iDMC Charter.

## 3.2 END OF STUDY

The end of the trial is defined as the date of the last visit of the last participating patient in this study. This is expected to occur 28 weeks after the last patient has been randomized into the study.

## 3.3 RATIONALE FOR THE STUDY DESIGN

This is a Phase IIIb/IV, two-arm, randomized, double-blind, placebo-controlled, parallel-group, international, multicentre trial. As detailed in Section 1.4, given the potential redundancy in the anti-inflammatory effects of GCs and that of the humanized anti-IL 6 receptor antibody TCZ, it is postulated that low-dose GCs do not contribute to the level of disease control achieved with TCZ to the same extent as observed during their co-administration with TNF inhibitors. The current study was therefore designed to assess whether GCs can be successfully tapered, and eventually discontinued during treatment with TCZ, while maintaining LDA (DAS28 ESR score ≤ 3.2) state.

The study will enrol both TCZ-experienced, and TCZ-naïve patients, who are inadequate responders to csDMARDs or bDMARDs. However, to allow for a comparable TCZ exposure before the prednisone tapering starts, patients with no prior exposure to TCZ will complete a 24 (or 28)-week Lead-in Phase, during which they will be treated with open label TCZ. Therefore patients will be entered and randomized into this study via two tracks; refer to Section 3.1 for details. To ensure adequate disease stability at a stable GC dose, criteria for randomization will include both a DAS28 ESR score ≤3.2 and a stable dose of 5 mg/day of Sponsor-provided open-label prednisone for ≥4 weeks prior to, and at the randomization visit.

To eliminate potential patient and physician bias, GC treatment will be tapered and discontinued in a double-blind manner, starting from a dose-level of 5 mg/day prednisone. This threshold was selected, because the potential contribution of GCs to disease control in patients who reached LDA state during treatment with TCZ is expected to diminish at or below the 5 mg/day prednisone dose.

The primary outcome measure is the change in disease activity (as assessed by DAS28 ESR) from randomization to Week 24 post-randomization; a validated measure that is widely used in clinical trials involving RA patients; refer to Section 3.3.4 for details.

## 3.3.1 Rationale for the Study Drug Dose and Schedule

### 3.3.1.1 Tocilizumab

A subcutaneous (SC) formulation of TCZ was developed to offer patients an additional option that may allow self-administration. The TCZ SC dose was selected based on pharmacokinetic/pharmacodynamics and limited efficacy and safety data from phase 1/2 studies, as well as the results of the recently published SUMMACTA trial. In this randomized, double-blind, Phase III, non-inferiority clinical trial enrolling 1262 patients with moderately to severely active RA who did not respond to a DMARD, TCZ 162 mg SC QW was non-inferior to TCZ 8 mg/kg IV Q4W (both in combination with DMARDs), by producing a comparable ACR20 response (primary efficacy endpoint) at Week 24: 69.4% (95% CI 65.5 to 73.2) versus 73.4% (95% CI 69.6 to 77.1), respectively (Burmester et al. 2014).

### 3.3.1.2 Prednisone

The criteria for randomization include a stable dose of 5 mg/day of prednisone at randomization and for at least 4 weeks prior to randomization. This dose is reflective of the most commonly used initial dose of prednisone in RA (Pincus et al. 2015), as well as the dose used by more than half of patients enrolled in clinical trials of biological drugs (Spies et al. 2011; Buttgereit 2012).

Randomized patients from both tracks will have been taking prednisone 5-15 mg/day (or GC equivalent) for at least 24 weeks prior to randomization.

Patients randomized to the blinded prednisone mock taper arm will continue to receive prednisone 5 mg/day for 24 weeks.

Patients randomized to the blinded prednisone taper arm will be tapered from 5 to 0 mg/day according to a fixed schedule, in 1 mg/day decrements every four weeks. Given that current guidelines do not address the tapering schedule for GCs in patients with RA, the current study is expected to provide valuable data regarding the proposed monthly tapering schedule.

## 3.3.2 Rationale for Patient Population

The selected study population comprises adults with at least 6-month history of RA diagnosed according to the ACR 1987 or ACR/EULAR 2010 criteria. The two-tier selection of study patients (TCZ-experienced patients enrolled via *Track TCZ-experienced patients* and TCZ-naïve patients enrolled via *Track TCZ-naïve patients*) is introduced to allow patients with no prior exposure to TCZ to be enrolled, upon completion of a 24- (or 28)-week Lead-in TCZ treatment period. To evaluate whether

LDA can be maintained despite GC tapering during treatment with TCZ, patients will have to reach and maintain LDA during 4 weeks before they are randomized.

### 3.3.3 Rationale for Control Group

Not applicable; in the current study a GC tapering schedule will be compared with no tapering.

### 3.3.4 Rationale for the Study Endpoints

Several disease activity measures are currently available; of these, the 28-joint disease activity score (DAS28) and the ACR response criteria are the most commonly used, including as primary endpoints in registrational trials. The efficacy outcome measures used in the current study have been selected based on their clinical relevance in assessing disease activity status, clinical improvement, or patient-assessed changes in functional status or quality of life in patients with RA. Each of the selected outcomes have been validated and previously used in RA clinical trials.

#### 3.3.4.1 28-Joint Disease Activity Score (DAS28)

The Disease Activity Score (DAS) (Van der Heijde et al. 1990) and its modified version including 28 joint count (DAS28) (Prevoo et al. 1995) were developed to measure disease activity in patients with RA at a given time point.

DAS28 has the following standardized cut-offs for disease activity and remission:

- DAS28 > 5.1 = high disease activity
- DAS28 between 3.2 and 5.1 = moderate disease activity
- DAS28 ≤ 3.2 = low disease activity
- DAS28 < 2.6 = remission

A score of DAS28 > 3.2 is an indication of disease active enough to reinforce treatment dosage or to switch the DMARD (Pincus et al. 2006; Fransen et al. 2004; Mäkinen et al. 2005).

The DAS28 is a validated clinical index of multiple measures, including a formal 28-joint count, an acute phase reactant measure [either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)], and a patient global assessment of disease activity (Prevoo et al. 1995). In the current study ESR will be used as acute phase reactant for determining the DAS28 ESR.

#### 3.3.4.2 CDAI and SDAI

The **CDAI** is a clinical assessment tool derived from the DAS28 and has high correlation to DAS28 scores (Smolen et al. 2003; Aletaha et al. 2005; Aletaha and Smolen, 2005). However, compared to DAS28, the CDAI is simpler to use and easier to calculate. The CDAI includes 28-joint counts (tender and swollen), patient and physician global assessment of disease activity, but does not require a blood test for evaluation of an acute phase reactant; therefore, complete results can be obtained and used to drive

treatment decisions at the same time as the patient's visit. The maximum total score for CDAI is 76.

The **SDAI** is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28-joint assessment), patient and physician global assessment of disease activity [visual analogue scale (VAS) 0-10 cm] and level of C-reactive protein (mg/dl, normal <1 mg/dl). The SDAI was validated on a total of 1,839 patients from three Phase 3 trials, and was found to correlate with a high level of statistical significance to the DAS 28 and HAQ scores. In addition, patients achieving the ACR 20, 50, 70 or 90% response showed proportionate changes in the SDAI (Smolen et al. 2003).

#### 3.3.4.3 ACR Core Set and Response Criteria

The American College of Rheumatology (ACR) Committee chose a core set of variables to be included in all RA clinical trials, by taking into account the sensitivity to change, the desire to eliminate redundant measures and attempting to select outcome measures that represented the breadth of RA manifestations. The ACR Core Set includes 7 disease activity measures: tender joint count [TJC], swollen joint count [SJC], patient's assessment of pain, patient's global assessment of disease activity, physician's assessment of physical function, patient's assessment of physical function, and an acute-phase reactant value (high sensitivity C-reactive protein [hsCRP] or ESR). In addition, for DMARD trial durations of 1 year or longer, radiography or other imaging technique is performed (Felson et al. 1993; Boer et al. 1994; Felson and LaValley, 2014).

The ACR definition of improvement in RA is a composite measure that can be used to categorize a patient as "improved" or "not improved" at one point in time compared with baseline. The ACR 20% improvement definition is based on 7 components and requires ≥ 20% improvement in both the TJC and the SJC and ≥ 20% improvement in ≥ 3 of the 5 secondary criteria: patient's global assessment of disease activity, physician's global assessment of disease activity, pain, physical function, and levels of an acute-phase reactant (Felson et al. 1995). The ACR 20% definition of improvement is considered the most widely used outcome measure in RA clinical trials (Felson and LaValley, 2014) and has been accepted by the US FDA as evidence of clinical efficacy of investigational antirheumatic drugs (FDA 1999).

#### 3.3.4.4 HAQ-DI

The disability section of the Stanford Health Assessment Questionnaire (**HAQ-DI**) is the most frequently used questionnaire worldwide to assess functional disability in RA patients. This measure of self-perceived disability contains 20 questions in eight categories and includes an additional section about aid from other people and devices needed to correct the disabilities recorded in the 20 questions, if applicable (Fries et al. 1982). Scores range from 0 to 3, with higher scores indicating worse disability. A decrease of at least 0.22 in the HAQ-DI is considered the threshold for clinically meaningful improvement.

#### 3.3.4.5 Rheumatoid Arthritis Impact of Disease (RAID) Questionnaire

Apart from patient-reported outcomes traditionally evaluated during the current standard assessment of RA (e.g. patient assessment of pain, functional disability and/or patient global assessment), other health domains are also important for the patient such as fatigue, wellbeing and sleep pattern. The Rheumatoid Arthritis Impact of Disease (RAID) score, a patient-reported composite index, was developed and validated under the umbrella of the EULAR (Gossec et al. 2009; Gossec et al. 2011; Heiberg et al. 2011; Boers 2011). The RAID comprises 7 domains (pain, function, fatigue, sleep, emotional well-being, physical well-being, and coping/self-efficacy), and evaluates the impact of RA on patient quality of life. Each of the 7 domains is evaluated as continuous variables on an 11-point Numerical rating scale (NRS), from 0 (best) to 10 (worst).

The range of the final RAID value is 0-10 where higher figures indicate worse status. A change of at least 3 points (absolute) or 50% (relative) in the RAID score is considered a minimum clinically important improvement, and a maximal value of 2 defines an acceptable status (Dougados et al. 2012).

#### 3.3.4.6 Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA)

The WPAI:RA is a 6-item questionnaire evaluating the effect of rheumatoid arthritis on the patient's ability to work and perform regular activities. The construct validity of a quantitative work productivity and activity impairment (WPAI) measure of health outcomes was tested for use in clinical trials, along with its reproducibility. All measures of work productivity and activity impairment were positively correlated with measures which had proven construct validity. Overall work productivity (health and symptom) was significantly related to general health perceptions and the global measures of interference with regular activity (Reilly et al. 1993).

### 3.3.5 Rationale for Biomarker Assessments

Rheumatoid arthritis is characterized by autoimmune-mediated attack of the joint synovial lining resulting in destruction of bone and cartilage, and is a clinically and biologically heterogeneous disease with respect to its course, response to therapy, and outcome (McInnes and Schett, 2011; Nam et al. 2014). Over the past years, significant progress has been made in the identification of biomarkers associated with response to biological DMARDs (Townsend, 2014). In particular, Dennis et al. demonstrated that response to TCZ was improved in patients with a "lymphoid" phenotype characterized by high levels of serum C-X-C motif chemokine 13 (CXCL13), and low levels of serum soluble intercellular adhesion molecule 1 (sICAM-1). They also showed that response to anti-TNF treatment was improved in RA patients with a "myeloid" phenotype characterised by high levels of sICAM-1 and low levels of CXCL13 (Dennis et al. 2014). Beside dynamic biomarkers (i.e. non-inherited biomarkers), response to TCZ in RA has been associated with genetic makeup of the patients (i.e. inherited biomarkers) (Wang et al. 2013).

Based on this data, we intend to assess whether dynamic (non-inherited) biomarkers are predictive of response to TCZ and/or glucocorticoids (i.e., predictive biomarkers),

susceptibility to developing adverse events, or progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of TCZ activity, or can increase the knowledge and understanding of disease biology. In addition, in the subset of patients who consent to DNA sampling, we will explore the possible association of inherited biomarkers with response to TCZ and/or glucocorticoids.

## 3.4 OUTCOME MEASURES

### 3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Change in DAS28 ESR between randomization and Week 24 post-randomization.

The key secondary efficacy outcome measure for this study is as follows:

- The proportion of patients with LDA (DAS28 ESR score ≤ 3.2) at Week 24 post-randomization, who have not suffered a flare due to RA and who showed no confirmed adrenal insufficiency that required replacement therapy.

Other secondary efficacy outcome measures for this study are as follows:

- Change in CDAI / SDAI between randomization and Week 24 post-randomization. The CDAI is composite score based on tender and swollen joint count, and the patient's and physician's assessment of global status. The SDAI includes the components of CDAI as well as CRP.
- The proportion or patients with ≥ 1 RA flare, the time to first RA flare and the number of RA flares.
- The proportion of patients with ≥ 1 administration of RA flare rescue medication, the time to first administration, and the number of administrations of RA flare rescue medication.
- Cumulative prednisone exposure (dose) between randomization and Week 24 post-randomization.
- The proportion of patients who maintain LDA (DAS28 ESR score ≤ 3.2) and the proportion of patients who maintain the baseline disease activity level at Week 24 post-randomization.
- The proportion of patients who permanently discontinue study treatment due to insufficient RA flare control.
- Changes in the ACR core set from randomization to post-randomization Week 24, including: swollen and tender joint counts; patient's assessment of pain and global status; physician's assessment of global status; HAQ-DI; and acute phase reactants (hsCRP and ESR).

### 3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Nature, frequency and severity of adverse events (graded according to CTCAE v4.0) including non-serious and serious adverse events, and adverse events of special interest.
- Changes in vital signs, physical findings, and clinical laboratory results during and following TCZ administration.
- Assessment of immunogenicity: Immunogenicity sampling will be "event-driven"; for patients who experience a hypersensitivity reaction (including anaphylaxis), additional samples will be taken and tested for anti-TCZ antibodies, plasma TCZ levels (PK) and sIL-6R (PD) at time of event and 8 weeks after the event, as part of the standard immunogenicity sampling protocol. No immunogenicity sampling is required in case of injection site reactions.
- Proportion of patients with confirmed adrenal insufficiency that required replacement therapy.

### 3.4.3 Patient-Reported Outcome Measures

In addition to the patient-reported components of the ACR core set and of other composite disease activity measures, the PRO outcome measures for this study include the following where translations are available:

- RAID score (measured at enrolment (*Track TCZ-naïve patients* only), randomization and at Week 24 post-randomization).
- HAQ-DI score (assessed at baseline, randomization and at Week 24 post-randomization).
- WPAI:RA score (assessed at enrolment (*Track TCZ-naïve patients* only), randomization and at Week 24 post-randomization).

### 3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- In a subset of the study population, levels of bone turnover biomarkers at relevant time points. The following bone turnover biomarkers will be tested: (i) Pro-collagen serum type I N-terminal propeptide (PINP), a marker of bone formation; and (ii) Serum C-terminal cross-linked telopeptide of type I collagen (CTX-I), a marker of cathepsin K-mediated bone collagen degradation believed to reflect systemic bone resorption.
- Measure of non-inherited biomarkers associated with RA biology and TCZ biology may include: serum C-X-C ligand 13 (CXCL13, also known as B cell–attracting chemokine 1), soluble intercellular adhesion molecule-1 (sICAM-1), serum matrix metalloproteinase-3 (MMP-3); and peripheral blood gene expression signatures for interferon (IFN)-induced genes and Plasmablast-associated genes.
- Change in the modified Homeostasis Model Assessment (HOMA1) from the beginning to the end of the Lead-in Phase (*Track TCZ-naïve patients* only) .

- Change in HOMA1 from randomization to the end of the study (Week 24; both tracks).

# 4. MATERIALS AND METHODS

## 4.1 PATIENTS

There are two target populations for this study:

***Track TCZ-experienced patients:*** Patients with a DAS28 ESR score ≤ 3.2 who are currently receiving TCZ (SC or IV) and 5 mg/day of prednisone (or GC equivalent). Eligibility criteria are evaluated during Screening, which starts up to 6 weeks prior to randomization.

***Track TCZ-naïve patients:*** Patients with moderate to severe active RA with an inadequate response to current csDMARD or bDMARD therapy and who require current treatment with 5 to 15 mg/day of prednisone (or GC equivalent). Eligibility criteria are evaluated during Screening, which starts up to 4 weeks prior to enrolment in the Lead-in Phase. Following treatment with TCZ and glucocorticoid taper (if clinically feasible) during the 24-Week Lead-Phase, these patients are eligible for randomization if they maintain a DAS28 ESR score ≤ 3.2 and stable prednisone 5 mg/day for at least 4 weeks prior to randomization.

### 4.1.1 Management of Enrolment to Achieve the Randomization Target

Study entry is possible via two tracks, *Track TCZ-experienced patients*, and *Track TCZ-naïve patients*. It is currently estimated that about 95% of patients from *Track TCZ-experienced patients* and about 50% of patients from *Track TCZ-naïve patients* will be eligible for randomization.

To mitigate potential over enrolment for the required randomization target, the actual vs estimated number of randomized patients will be closely monitored and adjustments to the ratios of the above formula may be made. A potential measure to avoid unnecessary prolongation of the study in case of slower than planned randomization would be to close enrolment of *Track TCZ-naïve patients*, and complete the remainder of the study by enrolling *Track TCZ-experienced patients* only. Conversely, if the enrolment of *Track TCZ-experienced patients* is as fast as or faster than that of *Track TCZ-naïve patients*, then fewer patients will be enrolled to achieve the randomization target.

### 4.1.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

*Track TCZ-experienced patients (study entry is enrolment following randomization):*

1. Able and willing to give written informed consent and comply with the requirements of the study protocol (including treatment on an outpatient basis).
2. Age ≥ 18 years.

3. RA of ≥ 6 months duration diagnosed according to the revised 1987 American College of Rheumatology (ACR, formerly the American Rheumatism Association) criteria or 2010 ACR / EULAR criteria.
4. Have received TCZ either SC (162 mg QW) or IV (8 mg/kg Q4W, not exceeding 800 mg/dose) for the treatment of RA for at least 24 weeks prior to randomization.
5. Have received 5 - 15 mg/day of prednisone (or GC equivalent) for the treatment of RA for at least 20 weeks prior to screening.
6. Currently receiving 5 mg/day of oral prednisone (or GC equivalent) at the Screening Visit.
7. Have a DAS28 ESR score ≤3.2 assessed 4 to 6 weeks prior to randomization (assessed at the Screening Visit or a visit prior to the Screening Visit).

*Track TCZ-naïve patients (study entry is enrolment into the Lead-in phase):*

1. Able and willing to give written informed consent and comply with the requirements of the study protocol (including treatment on an outpatient basis).
2. Age ≥ 18 years.
3. RA of ≥ 6 months duration diagnosed according to the revised 1987 ACR criteria or 2010 ACR / EULAR criteria.
4. Have active RA (defined as DAS28 ESR score > 3.2).
5. Are considered by the investigator as inadequate responders to csDMARDs or bDMARDs. Are TCZ treatment naïve or last TCZ treatment was > 12 months prior to screening and TCZ was not discontinued due to lack of efficacy, side effects, or any other safety reasons.
6. Are receiving 5 - 15 mg/day prednisone (or GC equivalent) for the treatment of RA.

### 4.1.3 Exclusion Criteria

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

*General*

1. Major surgery (including joint surgery) within 8 weeks prior to screening, or planned major surgery during the study and up to 6 months after randomization.
2. Pregnant women or nursing (breastfeeding) mothers.
3. In females of childbearing potential, a positive serum pregnancy test at screening.
4. Females of childbearing potential unwilling or unable to use a reliable means of contraception (e.g., physical barrier [patient or partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device) during study treatment and for a minimum of 3 months after the last dose of TCZ.
5. Body weight of ≥ 150 kg.
6. Lack of peripheral venous access.

*Disease-related*

7. RA of functional class IV, as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis (see Appendix 7).

8. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, or Felty syndrome). Secondary Sjögren syndrome with RA may be allowed per the discretion of the investigator.
9. Diagnosed with juvenile idiopathic arthritis or juvenile RA and/or RA before the age of 16 years.
10. Prior or current inflammatory joint disease other than RA (e.g., gout, Lyme disease, sero-negative spondyloarthropathy, including reactive arthritis, psoriatic arthritis, arthropathy of inflammatory bowel disease), or prior or current joint infections.
11. Previous history of primary or secondary adrenal insufficiency.

*Previous or Concomitant Prohibited Therapy*

12. Treatment with any investigational agent (tocilizumab excepted) within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening. Treatment with csDMARDs, other DMARDS, and/or biologics for RA which is permanently discontinued within 5 half-lives prior to randomization.
13. Previous treatment with any cell-depleting therapies, including investigational agents or approved therapies (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, anti-CD20).
14. Treatment with IV gamma globulin, plasmapheresis or Prosorba column within 6 months of screening.
15. Intraarticular (IA) or parenteral GCs within 6 weeks prior to randomization (within 12 weeks for intra-articular triamcinolone).
16. Previous treatment with oral or parenteral GCs for conditions other than RA, at any dose used continuously for > 1 week, during the last 1 year prior to screening. Current treatment with topical GC exceeding 20% of body surface area.
17. Immunization with a live/attenuated vaccine within 30 days prior to screening. Patients must agree not to take live attenuated vaccines (including seasonal nasal flu vaccine, varicella vaccine for shingles or chickenpox, vaccines for measles, mumps or rubella without or with varicella [MMR or MMRV], oral polio vaccine and vaccines for yellow fever), within 30 days before the Screening Visit, throughout the duration of the trial and for 60 days following the last dose of study drug.
18. Any previous treatment with alkylating agents such as chlorambucil or with total lymphoid irradiation.

*Laboratory Exclusion Criteria*

19. Inadequate haematological function indicated by any of the following:
    - White blood cells (WBCs) < 3.0 x $10^9$/L (3,000/$mm^3$).
    - Platelet count < 100 x $10^9$/L (100,000/$mm^3$).
    - Haemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L).
    - Absolute neutrophil count (ANC) < 2.0 x $10^9$/L (2,000/$mm^3$).
    - Absolute lymphocyte count < 0.5 x $10^9$/L (500/$mm^3$).

20. Inadequate renal function indicated by serum creatinine > 1.4 mg/dL (> 124 µmol/L) in female patients and > 1.6 mg/dL (> 141 µmol/L) in male patients.
21. Inadequate liver function indicated by any of the following:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 times the upper limit of normal (ULN).
    - Total bilirubin > ULN.
22. Positive hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab).

*Previous or Concomitant Conditions*

23. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies.
24. Evidence of current serious uncontrolled cardiovascular (including uncontrolled hyperlipidemia), nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or gastrointestinal (GI) disease.
25. Current liver disease as determined by the investigator.
26. History of diverticulitis, peptic ulcer disease, diverticulosis requiring antibiotic treatment, or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations.
27. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other opportunistic infections (including, but not limited to, tuberculosis [TB] and atypical mycobacterial disease, hepatitis B and C, Epstein-Barr virus, cytomegalovirus and herpes zoster, but excluding fungal infections of nail beds) on the day of enrolment. *Track TCZ-experienced patients* are exempt if they have an active mild infection which does not warrant a treatment interruption as per protocol Section 5.1.1.2 or local standard of care.
28. Neuropathies and/or other conditions that might interfere with pain evaluation (e.g. fibromyalgia) and/or are typically treated with systemic GCs unless related to primary disease under investigation.
29. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening
30. Active TB requiring treatment within the previous 3 years (patients previously treated for TB with no recurrence within 3 years are permitted). Patients failing to complete the TB evaluation (as per Appendix 9) by the end of screening are excluded.
31. History of or currently active, primary or secondary immunodeficiency.
32. Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including haematological malignancies and solid tumours, except basal and squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix uteri that was excised and cured), or breast cancer diagnosed within the previous 20 years.
33. History of alcohol, drug or chemical abuse within 1 year prior to screening.
34. Pre-existing central nervous system (CNS) demyelination or seizure disorders.

35. Any medical or psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial.

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be centralized and performed by means of an IxRS. Prior to entering the 24-week Tapering Phase, patients will be randomly assigned (1:1) to one of two treatment groups, either continuing 5 mg/day of prednisone or tapering prednisone in a double-blinded fashion.

Randomization will be stratified by the following factors:

- Baseline DAS28 ESR (< 2 / ≥ 2)
- Country/Region
- Concomitant DMARD treatment (monotherapy / combination therapy)
- Weight (< 60 kg, ≥ 60 kg – 100 kg, ≥ 100 kg)

The patient, investigator and study-related staff, the Sponsor and study monitors will be blinded to treatment assignment.

The study prednisone (active drug or placebo) will be provided as over-encapsulated tablets so that the active drug and placebo are undistinguishable in terms of appearance, smell and taste. See Section 4.3.1.2 for prednisone wallet distribution.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), 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 prednisone 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 serious adverse event). Patients who are unblinded will remain in the study and will continue to receive study treatment unless otherwise contraindicated.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study prednisone.

## 4.3 STUDY TREATMENT

The Sponsor provides all Investigational Medicinal Products (IMPs). The Sponsor does not provide non-IMP, with the exception of open-label prednisone (5 mg dose only).

**The IMPs to be used in this study are as follows:**

- Test Product: open label TCZ (SC and IV)

- Test Product: (blinded) Prednisone
- Comparator: (blinded) Placebo to prednisone

**Non-investigational medicinal products (non-IMPs) to be used in this study are as follows:**

- Permitted therapy (Section 4.4.1)
- Open label Prednisone or GC during the Screening Period, Lead-in Phase, or Tapering Phase (including open label prednisone as RA flare rescue medication).

### 4.3.1 Formulation, Packaging, and Handling

#### 4.3.1.1 Tocilizumab

Tocilizumab (SC and IV) will be supplied by the Sponsor throughout the Lead-in Phase (*Track TCZ-naïve patients* only), and throughout the Tapering Phase for both tracks.

Tocilizumab SC will be supplied in a 1-mL ready-to-use, single use pre-filled syringe with needle safety device. Each syringe delivers 162 mg (0.9 mL) of TCZ SC.

Tocilizumab IV will be supplied in vials (type I glass) with a stopper (butyl rubber) containing 10 ml concentrate for solution for infusion (sterile concentrate). Each ml of the concentrate contains 20 mg TCZ.

Tocilizumab (SC and IV) must be stored at 2 – 8 ºC (do not freeze) and protected from light. Details of the packaging and labelling of the TCZ are provided in the protocol-supporting documents.

For information on the formulation and handling of TCZ, see the Tocilizumab Investigator's Brochure and local prescribing information (as applicable).

#### 4.3.1.2 Prednisone

**Open-label prednisone tablets** will be:

- offered during the 4 weeks preceding randomization for patients in *both tracks*
- provided for the treatment of any RA flare following randomization (during the 24-week Tapering Phase).

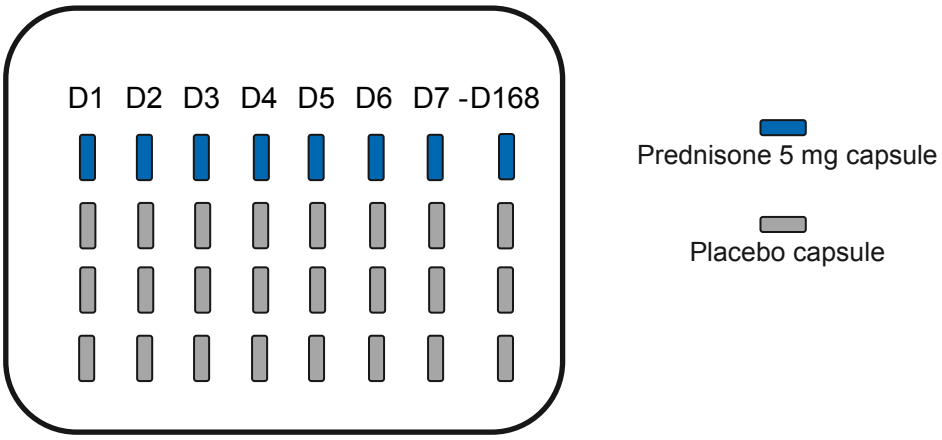
Prednisone tablets should be stored at temperatures below 25°C (77°F) in the original packaging in order to protect from light and humidity.

**Blinded study prednisone capsules** will consist of active prednisone ± placebo, and will be provided throughout the Tapering Phase in pre-packaged patient-identified wallets.

Prednisone capsules should be stored at room temperature below 30°C (86°F), and protected from moisture (Prednisone Prescribing Information, 2012). For information on handling prednisone, refer to the local prescribing information.

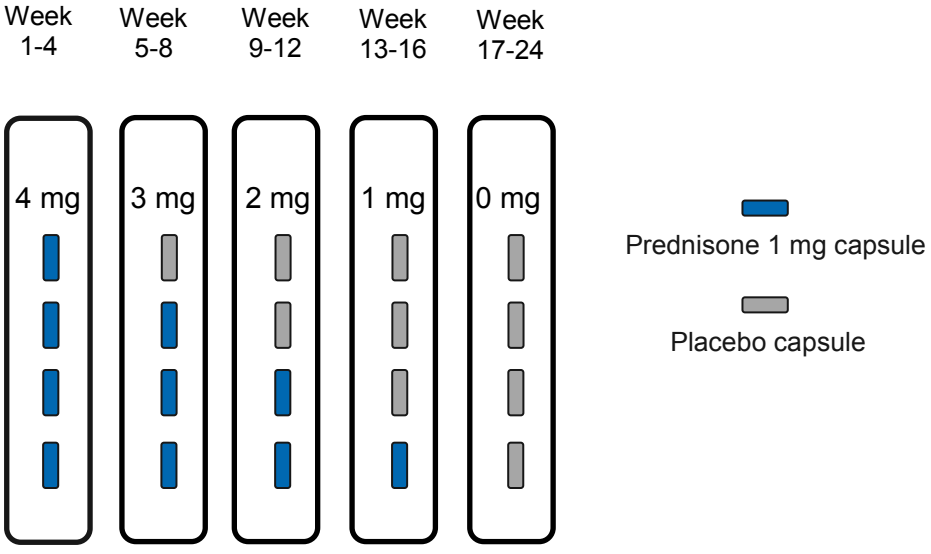
Patients who have been randomized to 5 mg/day of prednisone will receive 4 capsules of study prednisone every day, consisting of one 5 mg capsule and 3 placebo capsules (see Figure 5).

**Figure 5: Daily Prednisone Doses for patients continuing 5 mg/day of prednisone**




Patients randomized to tapered prednisone will have their active study prednisone replaced by an increasing amount of placebo capsules over the course of treatment (see Figure 6).

**Figure 6: Daily Prednisone Doses for patients on tapering prednisone**



Additional details of the packaging and labelling of study prednisone are provided in the protocol-supporting documents. For information on the formulation and handling of prednisone, please refer to the local prescribing information

### 4.3.2 Dosage, Administration, and Compliance

#### 4.3.2.1 Tocilizumab

The administration of TCZ is described according to study periods below.

- ***Screening and Randomization: Track TCZ-experienced patients***

This track consists of patients who are currently receiving TCZ (162 mg QW SC or 8 mg/kg Q4W IV, not exceeding 800 mg/dose). Patients must have received TCZ for at least 24 weeks prior to randomization. Patients receiving TCZ IV will have the option to be switched to TCZ SC (at the investigator's discretion) at the Randomization Visit, and this visit should coincide with the date of the next scheduled TCZ dose (or up to 4 days after the dose was due). TCZ SC initiation should be performed as per TCZ Administration instructions below.

- ***Lead-in Phase and Randomization: Track TCZ-naïve patients***

This track consists of patients who have not received any prior treatment with TCZ. Patients will enter a 24-week Lead-in Phase, during which time they will receive open-label TCZ SC at a dose of 162 mg QW or open-label TCZ IV at a dose of 8 mg/kg Q4W, not exceeding 800 mg/dose. The choice between TCZ SC or TCZ IV will be made by the investigator, depending on the local availability and individual patient acceptance and tolerability of the SC formulation. (Patients eligible for a 4-week extension of the Lead-in Phase, as per Section 3.1, will receive 28 weeks of open-label TCZ).

Patients transitioning from a previous bDMARD to TCZ (SC or IV) should receive their first TCZ dose at Lead-in Visit 1, and this visit should coincide with the date of the next scheduled administration of the previous bDMARD (or up to 7 days after the dose was due). Administration of TCZ (SC or IV) should be performed as per TCZ Administration instructions below.

- ***24-week Tapering Phase: All randomized patients***

During the 24-week Tapering Phase, randomized patients will receive open-label TCZ SC (162 mg QW) or TCZ IV (8 mg/kg Q4W, not exceeding 800 mg/dose).

- ***Post-study Treatment***

Management of patients completing the 24-week Tapering Phase will be according to local clinical practice at the discretion of the investigator. However, to ensure the scientific integrity of the study and to maintain the blind until database lock, it is recommended that patients completing the 24-week Tapering Phase continue treatment with TCZ (SC or IV) in addition to open-label prednisone to maintain disease control status.

***TCZ Administration Instructions (Lead-in Phase and Tapering Phase)***

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Any overdose or incorrect administration of TCZ should be noted on the Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of TCZ should be recorded on the Adverse Event eCRF.

*TCZ SC Administration:*

TCZ SC will be administered at the dose of 162 mg QW.

For SC TCZ use, the investigator should assess suitability of the patient for SC home use and instruct patients to inform a health care professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions.

During the Lead-in Phase and Tapering Phase, TCZ SC injections are given subcutaneously using a pre-filled syringe with a needle safety device. The recommended injection sites are in the front of the middle part of the thigh and the lower part of the abdomen below the navel (belly button), except for the 2 inch area directly around the navel. If a caregiver is giving the injection, the outer area of the upper arms could also be used. Injections are not to be administered to areas where the skin is not intact or is tender, bruised, red or hard.

The first-time ever injection of TCZ SC (initiation of TCZ SC) should be performed under the supervision of a qualified healthcare professional, and as per requirements for administration described in the local TCZ product information / package insert (if TCZ SC approved locally). Furthermore, patients and their caregivers should be trained to perform the TCZ SC injections at this visit. Once the patient or the patient's caregiver have demonstrated competence to administer the injection correctly, TCZ SC injections can be administered by the patient or the patient's caregiver at the site or at the patient's home. If a patient is unable or does not wish to administer TCZ SC at home, clinic staff can perform injections during a physician or clinic visit or at the patient's home.

Tocilizumab SC injections should be given on the same day every week whenever possible. If the weekly schedule cannot be met for any reason, injections can be given ≤ 2 days prior to the scheduled day, or ≤ 4 days after the scheduled day.

*TCZ IV Administration:*

TCZ IV will be administered at the recommended dose of 8 mg/kg body weight Q4W, not exceeding 800 mg/dose. TCZ IV infusions should be given within ± 4 days of the scheduled treatment day.

The medicinal product should be diluted to a final volume of 100 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique; refer to the local TCZ product information / package insert for details. After dilution, TCZ should be administered as an IV infusion over 1 hour.

All TCZ IV infusions will be administered at the clinical site, by a qualified healthcare professional, and as per requirements for administration described in the local TCZ product information / package insert.

#### 4.3.2.2 Prednisone and other Systemic Glucocorticoids

The administration of prednisone and other systemic glucocorticoids (GC) is described according to study periods below. A suggested glucocorticoid equivalence table is provided in Appendix 12.

- ***Screening: Track TCZ-experienced patients***

Prednisone or GC administered during Screening is non-IMP.

Patients are switched to Sponsor-provided open-label 5 mg/day prednisone at the Screening Visit and for the duration of the screening period, after signing informed consent, and only if they are currently on oral prednisone 5 mg/day or GC equivalent. Patients not on prednisone 5 mg/day (or GC equivalent) will have failed screening.

- ***Screening and Lead-in Phase: Track TCZ-naïve patients***

Prednisone or GC administered during the Screening or Lead-in phase is non-IMP.

Eligible patients must be receiving 5 to 15 mg of prednisone (or GC equivalent) per day at screening. Patients will enter a 24-week Lead-in Phase, during which time they will continue their open-label prednisone (or GC equivalent). During the Lead-in Phase, the dose of prednisone will be tapered down to 5 mg/day (if clinically feasible) according to a scheme determined by the investigator. All patients who are not on prednisone 5 mg/day (or GC equivalent) at Lead-in Week 20 are discontinued from the study.

- Patients on 5 mg/day of prednisone (or GC equivalent) and with a DAS28 ESR score ≤ 3.2 at Lead-in Week 20 must be switched to Sponsor-provided open-label 5 mg/day prednisone for the remainder of the Lead-in period (until Lead-in Week 24 / Randomization Visit).
- Patients who are on 5 mg/day of prednisone (or GC equivalent) and with a DAS28 ESR score > 3.2 at Lead-in Week 20 are discontinued from the study unless they have improved considerably (DAS28 ESR score < 4.4 and a change in DAS28 ESR score ≥1.2 compared to baseline). Considerably improved patients may continue in the Lead-in Phase and are re-assessed at Lead-in Week 24. If these patients are on 5 mg/day of prednisone (or GC equivalent) and have a DAS28 ESR score ≤ 3.2 at Lead-in Week 24, they must be switched to Sponsor provided open-label 5 mg/day prednisone for the remainder of the Lead-in period (until Lead-in Week 28 / Randomization Visit).

- ***24-week Tapering Phase: All randomized patients: Study Prednisone***

Study prednisone (defined as active prednisone ± placebo) is IMP.

*Track TCZ-experienced and Track TCZ-naïve* patients will be randomly assigned (1:1) to one of two treatment groups, to either continue or taper prednisone in a double-blinded fashion.

Patients randomized to tapered prednisone will receive 4 over-encapsulated tablets throughout the 24 weeks of Tapering Phase, consisting of a tapering dose of study prednisone, starting with 4 mg/day, with decrements of 1 mg every 4 weeks. Patients will have their study prednisone replaced with increasing amounts of placebo over the course of the Tapering Phase.

Patients randomized to continuing prednisone will receive 5 mg/day of study prednisone as 4 over-encapsulated tablets throughout the 24 weeks of Tapering Phase.

Study prednisone should be taken in the morning.

- ***24-week Tapering Phase: All randomized patients: RA Flare Rescue Prednisone***

Prednisone administered as a RA flare rescue medication is non-IMP.

Patients experiencing an RA flare during the 24-week Tapering Phase **must** be treated with Sponsor provided Flare Rescue Prednisone according to Section 4.5.11.

(Note: patients experiencing an RA flare during the Lead-in Phase are treated as per local practice).

- ***All Study Phases: Non-Sponsor Systemic Glucocorticoid Administration***

Non-Sponsor systemic GC (i.e. oral prednisone and other systemic GC compounds and formulations not provided by the Sponsor) administration is highly restricted:

  - *All Patients*: Use of intra-articular or parenteral GCs within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone) will disqualify the patient from randomization (as per: Exclusion Criteria Section 4.1.3).
  - *Track TCZ-naïve patients*: Non-Sponsor systemic GC (any route of administration) for any purpose (including RA) must not be used after 4 weeks prior to randomization and throughout the 24-week double-blind Tapering Phase. Only Sponsor-provided Study prednisone or RA flare rescue prednisone (see above) may be used; see Randomization Criteria (Section 4.5.10).
  - *Track TCZ-experienced patients*: Non-Sponsor systemic GC (any route of administration) for any purpose (including RA) must not be used after signed informed consent and throughout the 24-week double-blind Tapering Phase. Only Sponsor-provided Study prednisone or RA flare rescue prednisone (see above) may be used.

Short-term non-Sponsor systemic GC is permitted after randomization when deemed necessary for treatment or prevention of serious illness, in particular serious infections and adrenal insufficiency or adrenal crisis (see: Recommendations for Management of Adrenal Insufficiency Appendix 11). This administration will be made according to the medical judgment of the investigator, and should be documented in the eCRFs. Treatment should be stopped as soon as clinically safe.

Patients receiving any form of non-Sponsor systemic GC after randomization will be assessed by the Steering Committee to determine inclusion of these patients in the final per-protocol analysis, on a case by case basis.

- ***Post-study Treatment***

Management of patients completing the 24-week Tapering Phase, including treatment of any potential RA flares following completion of study treatment, will be according to local clinical practice at the discretion of the investigator. However, to ensure the scientific integrity of the study and to maintain the blind until database lock, it is recommended that patients completing the 24-week Tapering Phase be treated with open-label 3 mg/day of prednisone (and continue TCZ SC or IV) to maintain disease control status. Higher doses of GC, e.g. 5 mg/day of prednisone (or GC equivalent) may be required in patients who were receiving RA flare rescue medication at Week 24 post-randomization.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Patients will be required to document intake of the study medication in their daily diaries. Any overdose or incorrect administration of prednisone or study prednisone should be noted on the Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of prednisone or study prednisone should be recorded on the Adverse Event eCRF.

### 4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (TCZ SC, TCZ IV, and study prednisone) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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. The Drug Inventory Log will also be verified against the IMP administrations entered by the patients in their daily diaries.

### 4.3.4 Post-Trial Access to Tocilizumab SC or IV

Currently, the Sponsor does not have any plans to provide TCZ or any other study treatments or interventions to patients who have completed the study. For patients receiving TCZ SC during the Tapering Phase: the Sponsor will not continue to provide the TCZ SC formulation as patients will either revert to the TCZ IV formulation if the SC formulation is not yet available, or continue with the SC formulation if it is commercially marketed in their country.

The Sponsor will evaluate whether to continue providing TCZ in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

## 4.4 CONCOMITANT THERAPY

### 4.4.1 Permitted Therapy

Treatments considered necessary for the patient's benefit and not categorized as prohibited therapy are permitted. Important restrictions, prohibitions, or recommendations apply for several frequently administered therapies (see Section 4.4.1.1 through Section 4.4.1.7).

#### 4.4.1.1 Open-label csDMARDs

Patients receiving stable doses of csDMARDs prior to the initial Screening Visit (*Track TCZ-experienced* patients), at the Lead-in Week 20 Visit (*Track TCZ-naïve* patients on track for randomization at Lead-in Week 24), and at the extension Lead-in Week 24 (*Track TCZ-naïve* patients ineligible for randomization at Lead-in Week 24 but granted a 4 week Lead extension), should continue this treatment(s) going forward. Permitted csDMARDs are: hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine. **Dose increases or new csDMARD initiation is prohibited after the aforementioned visits**. Dose should be stable for at least 4 weeks prior to randomization, dose reductions or discontinuation may only be performed for safety reasons, and these changes must be documented in the eCRF.

Any overdose or incorrect administration of csDMARDs should be noted on the Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of csDMARDs should be recorded on the Adverse Event eCRF.

#### 4.4.1.2 Analgesics and Anti-inflammatories

(This section does not apply to glucocorticoids, see Section 4.4.1.6 below.)

Medications with analgesic and anti-inflammatory properties are permitted, as per clinical practice. These medications include NSAIDs, acetaminophen, opioids, and some other classes (e.g. anti-depressants, anti-convulsants).

Patients may be taking these medications as stable doses over the longer term. There is no additional guidance for these patients.

Alternatively, patients may be taking these medications sporadically or occasionally – these are often prescribed "as needed." For patients receiving occasional doses, if clinically feasible and safe, investigators should encourage patients to withhold these medications 12-24 hours prior to a visit where clinical efficacy assessments are performed and recorded (with the exception of the initial Screening Visit, since the patient informed consent is not yet signed).

#### 4.4.1.3 Proton Pump Inhibitors

Oral corticosteroids and NSAIDs are permitted during the study. Based on the current clinical evidence, it is generally recognized that the use of glucocorticoids and/or NSAIDs is associated with GI ulceration that may potentially lead to gastric perforation. Therefore, investigators should consider whether patients who receive glucocorticoids and/or NSAIDs should also receive prophylactic treatment with proton pump inhibitors (PPI) at a recommended dose or H2-receptor blockers at a maximum recommended dose.

#### 4.4.1.4 Glucocorticoid-Induced Osteopenia/Osteoporosis Therapy

Patients should receive oral calcium and 25-hydroxy vitamin D supplementation unless contraindicated (calcium 1200−1500 mg and vitamin D 800–1000 IU daily in divided doses). Unless contraindicated, bisphosphonate therapy (e.g., alendronate 70 mg weekly or zolendronate 4 mg annually) will also be administered at the discretion of the investigator for the prevention of glucocorticoid-induced osteoporosis. Participants with documented osteoporosis will be treated with approved drugs for osteoporosis according to local practice or clinical guidelines.

#### 4.4.1.5 Lipid-lowering Therapy

Use of lipid-lowering agents in patients with elevated lipids is strongly encouraged at any time during the study in conjunction with the investigator's clinical judgment and guidelines, such as those described in the third report from the National Cholesterol Education Program Adult Treatment Panel III (2002).

#### 4.4.1.6 Open-label Systemic Glucocorticoids

**Significant restrictions and prohibitions** are listed in Section 4.3.2.2.

#### 4.4.1.7 Drug Interactions Guidance for Permitted Therapy

The expression of hepatic CYP450 enzymes is suppressed by pro-inflammatory cytokines such as IL-6. Thus, it is expected that for any drug with a potent anti-cytokine inhibition such as TCZ, CYP450 suppression may be reversed when introduced in patients with rheumatoid arthritis. Investigators are advised that patients who are taking drugs which are individually adjusted and are metabolized via CYP3A4, CYP1A2, CYP2B6, CYP2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, cyclosporine, or benzodiazepines) should be monitored

during the first 2 weeks following start of TCZ treatment, and an increase in dose of these drugs may be necessary to maintain therapeutic effect. After cessation of TCZ treatment, patients should be monitored over 8 weeks to determine whether dose reduction may be needed (see Tocilizumab Investigator's Brochure for more details). For drugs metabolized by CYP2D6 and CYP2C19, no dose adjustment is anticipated.

The investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided (http://medicine.iupui.edu/clinpharm/ddis/table.aspx). In addition, the investigator should contact the Medical Monitor if questions arise regarding medications.

### 4.4.2 Prohibited Therapy

Treatment with the following medications or medication classes is prohibited.

- Therapies with washout periods and other prohibitions listed in the exclusion criteria (see Section 4.1.3) are prohibited during the Lead-in Phase (*Track TCZ-naïve)* and the Tapering Phase (both tracks).
- Initiation of a new csDMARD during the 4 weeks prior to randomization (See Section 4.4.1.1)
- Immunomodulating and immunosuppressant therapies with known efficacy in RA, and which are not expressly permitted, from the time of the initial Screening Visit or 4 weeks prior to randomization (whichever is longer). Permitted RA therapies are hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, and TCZ. Prohibited therapies include (but are not limited to):
    - Abatacept
    - Azathioprine
    - Cyclosporine
    - Gold
    - Tofacitinib
    - TNF-inhibitor biologics
    - Rituximab
- Significant restrictions and prohibitions regarding the use of systemic GCs are listed in Section 4.3.2.2.

## 4.5 STUDY ASSESSMENTS

Please see Appendix 1 (Screening and Lead-in Phase), Appendix 2 (24 Week Tapering Phase) and Appendix 3 (Early Treatment Discontinuations) for the Schedule of Assessments performed during the study.

### 4.5.1 Informed Consent Forms and Screening Log

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 patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before entering the study. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Patients may be re-screened or re-tested depending on the inclusion/exclusion criteria they fail and upon authorization by the Sponsor.

An Eligibility Screening Form 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.

In addition, the randomization criteria (see Section 4.5.10) must be completed and reviewed to confirm that patients meet all randomization criteria before being randomized. The investigator will maintain a log to record details of all patients entered into the study but not randomized, recording the reasons why patients were not randomized, if applicable.

### 4.5.2 Demographic Data and Medical History

Medical history includes clinically significant diseases, surgeries, RA history (including prior therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 4 weeks prior to the screening visit. NSAIDs will be recorded at screening as the average dose taken over the past 12 weeks.

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

### 4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study, changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.4 Vital Signs, Height, Weight and Body Mass Index

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position.

In addition, the patient's height (screening only) and body weight (screening and Week 24) will be measured, and body mass index (BMI) calculated.

### 4.5.5 Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from the Screening Visit through to the Safety Follow-up Visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

### 4.5.6 Laboratory, Biomarker, and Other Biological Samples

All laboratory, biomarker, and other biological samples are described below. The definitive schedule for obtaining these samples is the Table of Assessments, see Appendix 1, Appendix 2 and Appendix 3. The **Central Laboratory Services Manual** [redacted] provides specific technical instructions for collection, processing, storage and shipment of each type of sample.

**Mandatory Laboratory tests conducted by the Site or Local Laboratory:**

- Erythrocyte sedimentation rate (ESR) is performed **at the site** by the Westergren method and using kits provided by the central laboratory.
- Pregnancy test. All women who are not post-menopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening (Beta HCG) (Central Laboratory). Urine pregnancy tests will be performed at specified subsequent visits, and are conducted **at the site** using kits provided by the Central Laboratory. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (Central Laboratory).
- The patient may need confirmatory liver function testing in the event of an elevated liver function test finding which may lead to study drug discontinuation, as described in Section 4.6.2 and Section 5.1.1.7. The first sample should be sent to the **local laboratory** to facilitate rapid clinical decision making. Another sample (collected at the same time as the first sample) should be sent to the Central laboratory.
- Tuberculosis: Interferon gamma release assay (IGRA) (Central Laboratory) and/or the tuberculin skin test [TST] (**conducted at the site**) for tuberculosis; as per local practice and instructions in Appendix 9.

**Mandatory Laboratory tests sent to and conducted by the Central Laboratory:**

Fasting is mandatory:

- Fasting lipid panel (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides)
- Fasting C-peptide (serum)
- Fasting glucose (plasma)
- Fasting HbA1c (whole blood)

Patients will need to arrive for these tests in the fasted state. Patient should fast for 12 hours prior to the test. The patient may drink only water. Tea, coffee, diet drinks, or other beverages are not allowed. The patient should not smoke, chew gum, or exercise

during this time. Study medications are allowed only if scheduled. Other medications are allowed or prohibited during fasting as per investigator judgment.

Fasting not required:

- Rheumatoid factor (e.g latex test), anti-cyclic citrullinated peptide (anti-CCP) antibody
- High sensitivity C-reactive protein (hsCRP)
- HbSAg, HCV Ab (For *Track TCZ-experienced patients*, HbSAg and HCV Ab will only be tested in case of clinical suspicion based on history or clinical evidence of exposure.)
- Tuberculosis: IGRA (Central Laboratory) and/or the TST (conducted at site) for tuberculosis; as per local practice and instructions in Appendix 9.
- Haematology (white blood cell count, red blood cell count, haemoglobin, haematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells])
- Blood chemistry (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen [BUN] or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, lactate dehydrogenase [LDH]).
- 25-OH Vitamin D
- Urinalysis by “dipstick” method (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, red blood cells [RBCs], WBCs, casts, crystals, epithelial cells, bacteria).
- Pregnancy test. All women who are not post-menopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening (Beta HCG) (Central Laboratory). Urine pregnancy tests will be performed at specified subsequent visits, and are conducted at the site using kits provided by the Central Laboratory. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (Central Laboratory).
- Biomarker assessment, including bone turnover markers (PINP, CTX-I).
- Immunogenicity sampling is conducted for all patients during screening. For patients who experience a hypersensitivity reaction (including anaphylaxis) additional samples will be taken and tested for anti-TCZ antibodies, plasma TCZ levels (PK) and sIL-6R (PD) at time of event and 8 weeks after the event, as part of the standard immunogenicity sampling protocol. Blood samples will be sent to a Roche-approved designated laboratory for analysis of anti-TCZ antibodies, TCZ, IL-6 and sIL-6R concentration determination. See the **Central Laboratory Services Manual (**[redacted] for detailed instructions.
- RNA: whole blood samples for RNA extraction will be used for the analysis of gene expression including but not limited to gene signatures related to response to TCZ and to glucocorticoid.

- Protein biomarkers: serum samples will be used for the analysis of protein biomarkers including but not limited to CXCL13, sICAM-1, and MMP3.
- Serum cortisol may be measured after the last patient completes the study from stored leftover samples (if any) obtained for the other tests in this section.

**Optional Laboratory tests sent to and conducted by the Central Laboratory:**

The following tests are collected for the Research Biosample Repository (RBR) only if the patient has provided additional and separate consent and if other conditions are met, as detailed in Section 4.5.12:

- DNA: Whole blood for DNA extraction (genetic sampling).

### 4.5.7 Homeostasis Model Assessment

Homeostatic model assessment (HOMA) is a method for assessing β-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations (Matthews et al. 1985). The model has been widely used and validated since it was first published in 1985. It's validation included comparisons with a number of well-validated methods used to measure IR and β-cell function (Herman et al. 1999; Wallace et al. 2004).

Fasting C-peptide, a robust measure of insulin secretion, can substitute insulin in the HOMA model to assess IR (Wallace et al. 2004). In the current study, HOMA1 will be assessed using C-peptide as a measure of insulin secretion, at Lead-in Visit 1 (*Track TCZ-naïve patients only*), randomization and Week 24 (both tracks).

### 4.5.8 Evaluations of Rheumatoid Arthritis

This section lists the efficacy assessments which must be performed by the investigator. Assessments not performed by the investigator but required for analysis of outcomes are described at the end of this section.

#### 4.5.8.1 Swollen Joint Count and Tender Joint Count

Joints will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination (see Appendix 8). To ensure consistent joint evaluation throughout the study, individual patients should be evaluated by the same efficacy assessor for all study visits.

Joint prosthesis, arthrodesis or fused joints will not be taken into consideration for swelling or tenderness.

For clarification of how to assess joints which have undergone a procedure please see below:

- Surgery – joints which have been replaced or fused at any time prior to or at any time during the study should be documented as not evaluable (NE) for the duration of the study. Any joints which have undergone synovectomy at any time prior to or at any time during the study (including chemical and radiological synovectomy) should be documented as NE for the duration of the study.

- IA injection – Any joint which has received a steroid IA should be documented as not done (ND) for the following 12 weeks. After this time the joint may be assessed again.
- Arthrocentesis – Any joint which has fluid drained (and no steroid injected) will not be assessed at the next scheduled visit and will be graded as not done. After this time the joint may be assessed again.

#### 4.5.8.2 Physician's Global Assessment of Disease Activity VAS

The overall assessment of current disease activity will be made on a 100 mm horizontal VAS (see Appendix 10).

#### 4.5.8.3 DAS28 ESR

The DAS28 ESR is a combined index for measuring disease activity in RA. The DAS28 ESR scale ranges from 0 to 10, where higher scores represent higher disease activity.

The investigator will calculate the DAS28 ESR using the following formula:

$$\text{DAS28 ESR} = (0.56 \times \sqrt{(\text{TJC28})}) + (0.28 \times \sqrt{(\text{SJC28})}) + (0.7 \times \ln(\text{ESR})) + (0.014 \times \text{GH})$$

Where,

- TJC = tender joint count on 28 joints (Appendix 8)
- SJC = swollen joint count on 28 joints (Appendix 8)
- ln = natural log
- ESR = erythrocyte sedimentation rate (mm/hr) (Section 4.5.6)
- GH = general health, i.e., patient's global assessment of disease activity (100-mm VAS) (Section 4.5.9 and Appendix 10).

#### 4.5.8.4 Morning Stiffness

Morning stiffness will be collected at the visits defined in the schedule of assessments. The investigator will answer the following question in the eCRF:

- Does the patient's morning stiffness due to rheumatoid arthritis last longer than 15 minutes?

#### 4.5.8.5 Assessments not conducted at the site

The following assessments of RA are calculated and/or assessed during the analysis of outcomes based on the assessments and laboratory data collected during the study.

- American College of Rheumatology (ACR) Core Set and Response Criteria (see Section 3.3.4.3)
- Clinical Disease Activity Index (CDAI) (see Section 3.3.4.2)
- Simplified Clinical Disease Activity Index (SDAI) (see Section 3.3.4.2).

### 4.5.9 Patient-Reported Outcomes

Patient-reported outcomes (PRO) data will be collected via questionnaires to more fully characterize the patient's course of treatment. The questionnaires will be translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of all efficacy assessments and the administration of study treatment.

#### 4.5.9.1 Health Assessment Questionnaire - Disability Index (HAQ-DI)

The Stanford Health Assessment Questionnaire - Disability Index is a patient-completed questionnaire specific for RA. It consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities (Appendix 4).

#### 4.5.9.2 Rheumatoid Arthritis Impact of Disease (RAID) Questionnaire

The RAID is a patient-completed questionnaire specific for RA consisting of a 1-10 rating for pain, functional disability, fatigue, sleep, physical well-being, emotional well-being and coping. Scores are weighted to produce a final numerical result (see Appendix 5).

#### 4.5.9.3 Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis V2.0 or V2.1 (WPAI:RA)

The WPAI:RA is a patient-completed questionnaire. It consists of 6 questions to assess work productivity and activity impairment (see English US V2.0 in Appendix 6). Translations are available at: http://www.reillyassociates.net/WPAI_Translations-2.html. V2.1 should be used instead of V2.0 if available in local language.

#### 4.5.9.4 Patient's Global Assessment of Disease Activity VAS

The overall assessment of current disease activity will be made on a 100 mm horizontal VAS (see Appendix 10).

### 4.5.10 Randomization Criteria

Upon completion of the Screening Phase (*Track TCZ-experienced* patients) or the Lead-in Phase (*Track TCZ-naïve* patients), patients are eligible to be randomized for the study if they meet all of the following randomization criteria:

*Track TCZ-experienced* Patients Randomization Criteria

a) Fulfils all inclusion and none of the exclusion criteria;

b) Screening Visit occurred up to to 6 weeks prior to randomization;

c) DAS28 ESR score ≤ 3.2 at randomization;

d) Receiving prednisone 5 mg/day, and no other oral GC, at randomization and for ≥ 4 weeks prior to randomization;

e) Received no intra-articular or parenteral GCs within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone).

*Track TCZ-naïve* Patients Randomization Criteria

a) DAS28 ESR score ≤ 3.2 at most recent scheduled Lead-in Visit 4 weeks prior to randomization;

b) DAS28 ESR score ≤ 3.2 at randomization;

c) Receiving prednisone 5 mg/day, and no other oral GC, at randomization and for ≥ 4 weeks prior to randomization;

d) Received no intra-articular or parenteral GCs within 6 weeks prior to randomization (within 12 weeks prior to randomization for intra-articular triamcinolone).

### 4.5.11 RA Flare Assessment and Treatment (24 Week Tapering Phase)

For patients experiencing an RA flare (detected during a scheduled or unscheduled visit), defined as an increase in DAS28 ESR > 0.6 from the randomization visit value and a current DAS28 ESR > 3.2, TCZ and study prednisone will continue to be dispensed as planned and the blind maintained.

In addition, patients will receive a 2-week course of RA flare rescue medication, consisting of 5 mg of open-label prednisone daily. The patient will be asked to come for a Flare Assessment Visit at the end of this 2-week course.

If the patient's RA is still active (DAS28 ESR > 3.2) at this visit, this will be considered to be a second RA flare and a second 2-week course of RA flare rescue medication should be initiated, consisting of 5 mg of open-label prednisone daily.

At the end of this second 2-week course, the patient will be re-assessed at another Flare Assessment Visit. If the patient's RA is still active (DAS28 ESR > 3.2) at this visit, the patient will attend a Study Treatment Discontinuation Visit, followed in 4 weeks by a Safety Monitoring Visit. Note that if the end of either 2-week course of RA flare rescue medication coincides with a standard planned study visit, a separate Flare Assessment Visit does not need to be completed. These patients will be subsequently treated according to local clinical practice at the discretion of the investigator and encouraged to attend a Limited Week 24 Assessment Visit, at 24 weeks post-randomization (see Appendix 3).

The investigator may opt to not treat DAS28-ESR elevation formally meeting the RA flare criteria in the exceptional circumstance that the elevation is not due to RA flare (e.g. prominent ESR elevation due to acute infection and not due to RA). In this case, the investigator must enter an associated adverse event in the eCRF.

### 4.5.12 Samples for Research Biosample Repository

#### 4.5.12.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used 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 RBR 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 for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease worsening
- 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.

#### 4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to 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 (Section 4.5.12) will not be applicable at that site.

#### 4.5.12.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to TCZ mode of action, IL-6 biology, GC biology, RA biology, or biology of related diseases:

- Residual serum
- Residual whole blood for RNA extraction.

The following samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to TCZ mode of action, IL-6 biology, GC biology, RA biology, or biology of related diseases:

- Whole blood for DNA extraction (genetic sampling). In the current study, collection of whole blood for DNA extraction will be optional, i.e. it will be performed in a subset of the study population.

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 laboratory manual.

RBR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 4.5.12.4 and Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

#### 4.5.12.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RBR specimens and associated data. Upon receipt by the RBR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labelled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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 be disclosed to third parties only 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 research conducted using RBR specimens will be available in accordance with the effective Roche policy on study data publication.

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

#### 4.5.12.5 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 RBRResearch Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

#### 4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR 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 through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample 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 MA29585 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 MA29585.

#### 4.5.12.7 Monitoring and Oversight

RBR specimens 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 the RBR 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 RBR samples.

## 4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for 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

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. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study after randomization will not be replaced.

### 4.6.2 Study Treatment Discontinuation

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

- Pregnancy
- Anaphylaxis or serious hypersensitivity (Immunogenicity testing required, see Section 4.5.6)
- Gastrointestinal perforation
- Persistent increases in ALT and/or AST > 3 x ULN, confirmed by repeat testing (see Section 5.1.1.7) (repeat testing sample may be sent to a local laboratory to facilitate rapid medical decision making)
- First occurrence of ALT and/or AST elevation > 5 x ULN, after value confirmed by repeat testing (see Section 5.1.1.7) (repeat testing sample may be sent to a local laboratory to facilitate rapid medical decision making)
- Criteria meeting the definition of Hy's Law: ALT or AST elevation > 3 x ULN and total bilirubin elevation > 2 x ULN without initial findings of cholestasis (such as elevated alkaline phosphatase)
- ANC < 0.5 x $10^9$/L
- Platelet count < 50 x $10^3$/µL
- Malignancies (except local basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix uteri that have been excised and cured)
- Central demyelinating event
- Two consecutive RA disease flares post-randomization not responding to treatment as described in Section 4.5.11.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Any patient who permanently and prematurely discontinues IMP (TCZ or study prednisone) during the Lead-in or Tapering Phase will attend a Study Treatment Discontinuation Visit, followed in 4 weeks by a Safety Monitoring Visit. Randomized patients are encouraged to attend a Limited Assessment Week 24 Visit, at 24 weeks post-randomization. These visits and waivers to these visits are detailed in Appendix 3.

Any patient who prematurely discontinues study medication will be subsequently treated according to local clinical practice at the discretion of the investigator.

### 4.6.3 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 enrolment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing 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
- No study activity (i.e., all patients have completed and all obligations have been fulfilled).

## 5. ASSESSMENT OF SAFETY

### 5.1 SAFETY PLAN

Adherence to the planned study drug dose regimen is required unless an adjustment is necessary for safety reasons. The following sections provide an overview of the main risks and precautions associate with the use of the study drugs, including risk mitigation and dose modification rules, where applicable.

### 5.1.1 Precautions Related to Treatment with Tocilizumab

#### 5.1.1.1 Hypersensitivity reactions

Serious hypersensitivity reactions have been reported in association with infusion of TCZ. Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous infusions even if they have received premedication with steroids and antihistamines. For IV TCZ use, appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during the IV administration of TCZ. For SC TCZ use, suitability of the patient for SC home use should be assessed and patients should be instructed to inform a health care professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of

serious allergic reactions. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of TCZ should be stopped immediately and TCZ should be permanently discontinued.

#### 5.1.1.2 Infection and Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including TCZ. Tocilizumab treatment must not be initiated in patients with active infections. Administration of TCZ should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of TCZ in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections.

#### 5.1.1.3 Tuberculosis

As recommended for other biological treatments, RA patients should be screened for latent TB infection prior to starting TCZ therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating TCZ. Patients should be instructed to report if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a TB infection occur during or after therapy with TCZ. See Appendix 9 for details.

#### 5.1.1.4 Gastrointestinal Perforation

Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with TCZ in RA patients. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

#### 5.1.1.5 Demyelinating Disorders

The potential for central demyelination with TCZ is currently unknown. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Physicians should exercise caution in considering the use of the study medications in patients with pre-existing or recent onset demyelinating disorders. Treatment with the study medications should be interrupted during assessment of a potential demyelination event and only resumed if the benefit of continuing study drug is favourable.

#### 5.1.1.6 Viral Reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA.

#### 5.1.1.7 Active Hepatic Disease, Hepatic Impairment, Hepatic transaminase elevations

Treatment with TCZ, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases. In RA patients, ALT and AST levels

should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, TCZ treatment should be interrupted. For recommended modifications based on transaminases see Table 2.

**Table 2: Treatment Modifications in Case of Elevations in ALT & AST**

| ALT and/or AST | Action |
|---|---|
| > 1* to 3 x ULN | Dose-modify concomitant DMARDs if appropriate.<br>TCZ SC:<br>• For persistent increases in this range, reduce TCZ dose frequency to every other week injection or interrupt TCZ until ALT or AST have normalised.<br>• Restart with weekly or every other week injection, as clinically appropriate.<br>TCZ IV:<br>• For persistent increases in this range, reduce TCZ dose to 4 mg/kg or interrupt TCZ until ALT or AST have normalised.<br>• Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate. |
| > 3 to 5 x ULN | Interrupt TCZ dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN.<br>For persistent increases > 3 x ULN (confirmed by repeat testing), discontinue TCZ. |
| > 5 x ULN | Confirm value by repeat testing.<br>Discontinue TCZ. |
| > 3 x ULN and Other Criteria** (Hy's Law) | Discontinue TCZ. |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TCZ: tocilizumab; ULN: upper limit of normal

* ULN or patient's baseline, whichever is higher.

** Other criteria: total bilirubin elevation > 2 x ULN without initial finding of cholestasis (such as elevated alkaline phosphatase.

Patients withdrawn from the study due to elevated liver function tests must have repeat tests performed, as clinically appropriate, until levels return to baseline. If the patient's liver function tests have not returned to baseline within 6 months (or sooner, if deemed necessary by the investigator), an ultrasound and/or liver biopsy should be considered.

If a liver biopsy is performed for any reason, the biopsy report should be forwarded to Roche and the prepared histologic slides will be requested by Roche and centrally reviewed by a third party.

### 5.1.1.8 Haematological Abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with TCZ 8 mg/kg in combination with MTX. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. Severe neutropenia may be associated with an increased risk of serious infections. For recommended dose modifications based on ANC, see Table 3.

**Table 3: Treatment Modifications in Case of Decreases in Neutrophil Count**

| ANC (cells x $10^9$/L) | Action to Be Taken |
|---|---|
| > 1 | Maintain dose |
| 0.5 – 1 | Interrupt TCZ dosing.<br>TCZ SC:<br>• When ANC increases > 1 x $10^9$/L, resume TCZ dosing every other week and increase to every week injection, as clinically appropriate.<br>TCZ IV:<br>• When ANC increases > 1 x $10^9$/L, resume TCZ at 4 mg/kg and increase to 8 mg/kg, as clinically appropriate. |
| < 0.5 | Discontinue TCZ |

ANC: absolute neutrophil count; TCZ: tocilizumab

Patients withdrawn from the study due to a reduced neutrophil count must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, and must have a repeat WBC count with differential performed weekly until the ANC is above 1.0 x $10^9$/L (1000 cells/mm³). If the ANC does not return to above 1.0 x $10^9$/L (1000 cells/mm³) within 2 months (or sooner if deemed necessary by the investigator), a haematology referral is recommended.

For recommended dose modifications based on platelet counts, see Table 4.

**Table 4: Treatment Modifications in Case of Decreases in Platelet Count**

| Platelet count (cells x $10^3$/µl) | Action to Be Taken |
|---|---|
| > 100 | Maintain dose |
| 50 – 100 | Interrupt TCZ dosing.<br>TCZ SC:<br>• When platelet count increases > 100 x $10^3$/µL, resume TCZ dosing every other week and increase to every week injection, as clinically appropriate.<br>TCZ IV:<br>• When platelet count increases > 100 x $10^3$/µL, resume TCZ at 4 mg/kg and increase to 8 mg/kg, as clinically appropriate. |
| < 50 | Discontinue TCZ |

Patients withdrawn from the study due to a reduced platelet count must repeat platelets weekly until the count is above 100 x $10^3$/µL (100,000 cells/mm³). If the platelets do not return to above 100 x $10^3$/µL (100,000 cells/mm³) within 2 months (or sooner if deemed necessary by the investigator), a haematology referral is recommended.

### 5.1.1.9 Elevated Lipid Parameters

Elevations in lipid parameters including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were observed in patients treated with TCZ. In the majority of patients, there was no increase in atherogenic indices, and elevations in total

cholesterol responded to treatment with lipid lowering agents. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

#### 5.1.1.10 Other Potential Risks

The risk of malignancy is increased in patients with RA, and immunomodulatory medicinal products may increase the risk of malignancy.

Live and live attenuated vaccines should not be given concurrently with TCZ, as clinical safety has not been established.

### 5.1.2 Precautions Related to Glucocorticoid Use

Rare instances of anaphylactoid reactions have occurred in patients receiving GC therapy.

**Cardio-Renal:**

GCs can cause elevation of blood pressure, salt and water retention, increased excretion of potassium, and increased calcium excretion. Literature reports also suggest an apparent association between use of GCs and left ventricular free wall rupture after a recent myocardial infarction.

**Endocrine**:

GCs can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment, which may persist for up to 12 months after discontinuation of therapy.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients.

**Infections**:

Prednisone is contraindicated in systemic fungal infections.

Patients who are on GCs are more susceptible to infections than are healthy individuals. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of GCs alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but may be severe and at times fatal. With increasing doses of GCs, the rate of occurrence of infectious complications increases. GCs may also mask some signs of current infection.

If GCs are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. Chickenpox and measles can have a more serious or even fatal course in patients on GCs.

**Vaccines**:

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of GCs. Killed or inactivated vaccines may be administered. However, the response to such vaccines may be diminished and cannot be predicted.

**Ophthalmic:**

Use of GCs may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi or viruses.

For further details regarding the warnings and precautions related to GC use, refer to the local prescribing information.

### 5.1.3 Management of Specific Adverse Events

Guidelines for management of specific laboratory abnormalities are outlined in Table 2, Table 3 and Table 4.

#### 5.1.3.1 Management of Adrenal Insufficiency

As noted in Section 5.1.2, GCs can produce reversible HPA axis suppression with the potential for adrenal insufficiency after the beginning of glucocorticoids tapering which may persist for up to 12 months. Patients will be informed about this risk, and should be educated on reporting symptoms suggestive of adrenal insufficiency.

Management of potential adrenal insufficiency in study patients will be at the investigator's discretion. In case of a clinical suspicion of adrenal insufficiency, a short ACTH stimulation test may be performed, preferably before initiation of replacement treatment. Recommendations for the management of adrenal insufficiency are provided in Appendix 11, however their use is optional.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting 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 5.4.

### 5.2.1 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 unfavourable 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 5.3.5.10

- 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).

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is 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 5.3.5.11)
- 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)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a 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 (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section 5.3.3); 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).

### 5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest (AESI) 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). Any non-serious event in a tocilizumab AESI category that the investigator judges to be of special interest with regard to the benefit-risk or safety profile for tocilizumab, should be identified by the investigator as a tocilizumab AESI. Adverse events of special interest categories for this study include the following:

- Serious and/or medically significant infections, including all opportunistic infections and non-serious infections as defined by those treated with IV anti-infectives
- Suspected transmission of an infectious agent by TCZ, 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.
- Myocardial infarction / acute coronary syndrome
- Gastrointestinal perforations, including related fistulae and related intra-abdominal abscesses
- Malignancies
- Anaphylaxis / hypersensitivity reactions
- Demyelinating disorders
- Stroke, including transient ischemic attack events
- Serious and/or medically significant bleeding events requiring transfusion, or bleeding with hospital visit for evaluation (including emergency department or outpatient clinic)
- Serious and/or medically significant hepatic events, including:
  - events with a hepatic clinical diagnosis
  - hepatic abnormality resulting in permanent discontinuation of TCZ
  - cases of potential drug-induced liver injury, including cases meeting the definition of Hy's Law as per Section 4.6.2, and repeated here:
    - ALT or AST elevation > 3 x ULN and total bilirubin elevation > 2 x ULN without initial findings of cholestasis (such as elevated alkaline phosphatase).

### 5.2.4 Selected Adverse Events

Not applicable.

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 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 and in the Adverse Event eCRF page.

**After informed consent** has been obtained **but prior to the initiation of treatment** (*Track TCZ-experienced patients* – prior to the initiation of treatment in the Tapering Phase; *Track TCZ-naïve patients* – prior to the initiation of treatment in the Lead-in Phase), only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

**After the initiation of treatment** (*Track TCZ-experienced patients* – after the initiation of treatment in the Tapering Phase; *Track TCZ-naïve patients* – after the initiation of treatment in the Lead-in Phase), all adverse events will be reported until 4 weeks after the last dose of TCZ / study prednisone. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (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

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 5: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c] |
| 4 | Life-threatening consequences or urgent intervention indicated [d] |
| 5 | Death related to adverse event [d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.
d. Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

### 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 (as applicable)
- 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 patients 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 in the Adverse Event eCRF page. Avoid colloquialisms and abbreviations.

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

#### 5.3.5.1 Injection Site Reactions and Infusion Reactions

Adverse events that occur during or within 24 hours after TCZ administration and are judged to be related to TCZ injection (TCZ SC) or infusion (TCZ IV) should be captured as a diagnosis (e.g., "injection-site reaction" or “infusion reaction”, respectively in the Adverse Event eCRF page. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded in the dedicated Injection/Infusion Reaction eCRF page. If a patient experiences both a local and systemic reaction to the same dose of TCZ, each reaction should be recorded separately in the Adverse Event eCRF page, with signs and symptoms also recorded separately in the dedicated Injection/Infusion Reaction eCRF page.

#### 5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded in the Adverse Event eCRF page 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 in the Adverse Event eCRF page. 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.

#### 5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are 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. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event in the Adverse Event eCRF page. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported in the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately in the eCRF.

- If a severe gastrointestinal haemorrhage leads to renal failure, both events should be reported separately in the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately in the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately in the eCRF.

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

#### 5.3.5.4 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 in the Adverse Event eCRF page. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded in the Adverse Event eCRF page. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF page should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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 as a separate event in the Adverse Event eCRF page.

#### 5.3.5.5 Abnormal Laboratory Values

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

- Is 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 hypokalaemia) or a change in concomitant therapy
- Is 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 x ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the Adverse Event eCRF page.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the Adverse Event eCRF page, 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 "hyperkalaemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the Adverse Event eCRF page (see Section 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.6 Abnormal Vital Sign Values

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

- Is 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
- Is 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 in the Adverse Event eCRF page.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the Adverse Event eCRF page (see Section 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.7 Abnormal Liver Function Tests

The following finding (as defined by Hy's law) is considered to be an indicator of severe liver injury:

- ALT or AST elevation > 3 x ULN and total bilirubin elevation > 2 x ULN without initial findings of cholestasis (such as elevated alkaline phosphatase).

A patient with these findings must be discontinued from study medication as per Section 4.6.2.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the Adverse Event eCRF page (see Section 5.3.5.2) 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 an adverse event of special interest (see Section 5.2.2, Section 5.2.3 and Section 5.4.2).

#### 5.3.5.8 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 in the Adverse Event eCRF page and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to worsening of rheumatoid arthritis.

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 in the Adverse Event eCRF page. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after 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 in the Adverse Event eCRF page. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to worsening of rheumatoid arthritis, this should be recorded in the Adverse Event eCRF page.

#### 5.3.5.9 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded in the General Medical History and Baseline Conditions eCRF page.

A pre-existing 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 in the Adverse Event eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

#### 5.3.5.10 Lack of Efficacy or Worsening of Rheumatoid Arthritis

Events that are clearly consistent with the expected pattern of progression of the underlying disease (i.e. worsening of RA) should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of worsening will be based on ACR criteria. Every effort should be made to document the worsening of RA through use of objective criteria. If there is any uncertainty as to whether an event is due to the worsening of RA, it should be reported as an adverse event.

#### 5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a pre-existing 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 experienced 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.

#### 5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded in the Adverse Event eCRF page. If the associated adverse event fulfils 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 5.4.2).

Limited safety data related to overdosing of TCZ are available (see Tocilizumab Investigator's Brochure).

#### 5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event 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 (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

### 5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

#### 5.4.2.1 Events That Occur Prior to Initiation of Treatment

After informed consent has been obtained but prior to the initiation of treatment (*Track TCZ-experienced patients* – prior to the initiation of treatment in the Tapering Phase; *Track TCZ-naïve patients* – prior to the initiation of treatment in the Lead-in Phase), 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 Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

#### 5.4.2.2 Events That Occur after Initiation of Treatment

After initiation of treatment (*Track TCZ-experienced patients:* after the initiation of treatment in the Tapering Phase; *Track TCZ-naïve patients:* after the initiation of treatment in the Lead-in Phase), SAEs and adverse events of special interest will be reported until 4 weeks after the last dose of TCZ / study prednisone. Investigators should

record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) in the Adverse Event eCRF page and submit the report via the electronic data capture (EDC) system.

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 Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

### 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 6 months of the last dose of TCZ / study prednisone. A Pregnancy Report Form provided to investigators should be completed and submitted to the Sponsor immediately (i.e., no more than 24 hours after learning of the pregnancy) either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded in the Adverse Event eCRF page. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the foetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported in the Adverse Event eCRF page.

#### 5.4.3.2 Pregnancies in Female Partners of Male Patients

Not applicable.

#### 5.4.3.3 Abortions

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

#### 5.4.3.4 Congenital Anomalies/Birth Defects

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

## 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 in the Adverse Event eCRF page and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. Reporting instructions provided in Section 5.4.3.1 should be followed.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, 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 Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as until 4 weeks after the last dose of TCZ / study prednisone), if the event is believed to be related to prior IMP treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest 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 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 documents:

- Tocilizumab Investigator's Brochure
- United States Product Insert for prednisone.

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.

An iDMC will monitor the incidence of the above-listed anticipated events during the study.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The present section outlines the planned statistical analysis of the study. Full details will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to locking of the study database at the end of the study. The SAP may include exploratory analyses not explicitly mentioned in this section.

The main analysis of efficacy and safety will be comparative and concern the two arms of the Tapering Phase. The present section will mainly focus on this part of the study. The lead-in phase will be evaluated separately and details of specific analyses including both phases, in particular of key safety variables, will be provided in the SAP.

The main analysis populations will be defined as follows:

- **Full Analysis Set (FAS):** all included patients.
- **Safety population**: all patients receiving at least one dose of any of the study medications in the Tapering Phase, with patients grouped according to the treatment actually received during this phase.
- **Intent-to-treat (ITT) population**: all randomized patients, with patients grouped according to the treatment assigned at randomization.
- **Per-Protocol (PP) population**: subset of the ITT population excluding patients not fulfilling one or more of the criteria for randomization and patients with other protocol violations described in the SAP, grouped according to the treatment actually received during the randomized phase.

Unless otherwise indicated, all statistical hypotheses will be tested at the 5% significance level (i.e. no correction for multiple testing will be employed), and against two-sided alternatives. Corresponding 95% confidence intervals will be provided as appropriate.

## 6.1 DETERMINATION OF SAMPLE SIZE

This study primarily focuses on estimation rather than formal hypothesis testing. A sample size of 226 randomized patients is expected to provide > 80% power to produce a two-sided 95% confidence interval with a half-width < 0.5 DAS28 ESR units. The calculation is based on a two-sided *t*-test for a difference between the two arms and assumes a standard deviation of 1.33 units (conservative assumption based on data under stable TCZ treatment) and an analysis in the ITT population. Differences < 0.6 DAS28 ESR units would be considered of marginal clinical importance. There are no

reference data for an accurate assumption regarding the expected between-arm difference, but assuming an observed difference of < 0.25 units (mean disease activity is expected to slightly decrease in the steroid taper arm and to be stable in the placebo-taper arm), the two-sided 95% confidence interval will exclude differences between the two arms > 0.6.

For 226 patients to be randomized, taking into account that approximately 50% of included patients are expected to be "Lead-in failures" (i.e. not meeting the randomization criteria for *Track TCZ-naïve patients*), up to approximately 450 patients will need to be included into the study.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

Descriptive statistics will be used in evaluating the conduct of the study. Variables evaluated in this analysis will include the rate and reasons of screening failure, the dropout rate prior to randomization for the two tracks and during the Tapering Phase, and the frequency and type of protocol violations.

Compliance with study medication (including medication errors) will be summarized.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Unless indicated otherwise, for the analysis of the randomized phase, the assessments at the randomization visit will constitute baseline.

To assess the comparability of treatment arms at baseline, a descriptive analysis of relevant background information, including demographic data, medical history, concomitant treatment and baseline data, will be performed by treatment arm for the ITT population.

## 6.4 EFFICACY ANALYSES

The primary analysis population for the primary and secondary efficacy analyses will be the ITT population. Supportive analyses of the primary endpoint, of the key secondary endpoint and of other selected secondary endpoints will be conducted in the PP population.

### 6.4.1 Primary Efficacy Endpoint

The statistical analysis will assess the difference between the two arms in terms of change in DAS28 ESR score from baseline to Week 24 post-randomization. The between-group comparison will be performed based on an analysis of covariance (ANCOVA) model including the baseline DAS28 ESR score and other stratification factors applied at randomization.

For ITT patients who are prematurely withdrawn from treatment during the 24-week Tapering Phase, the DAS28 ESR value at the time of study treatment discontinuation will be used in the analysis. For ITT patients who are on RA flare rescue medication at Week 24 post-randomization, the DAS28 ESR value at the time of rescue medication start will be used in the analysis.

### 6.4.2 Secondary Efficacy Endpoints

The analysis of secondary efficacy endpoints will be exploratory.

The key secondary efficacy analysis (comparison of the proportion of patients with LDA (DAS28 ESR score ≤ 3.2) at Week 24 post-randomization, who have not suffered a flare due to RA and who showed no confirmed adrenal insufficiency that required replacement therapy) will be carried out by means of a logistic regression model including the same explanatory variables used for the analysis of the primary efficacy endpoint.

Disease activity measures such as CDAI, SDAI and HAQ-DI will be analysed as described for the primary efficacy endpoint. Details of the analysis methodology for other secondary endpoints will be provided in the SAP.

## 6.5 SAFETY ANALYSES

Safety will be assessed in the safety population in terms of adverse events, clinical laboratory results, physical examination, and vital signs. Adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. For adverse events of special interest, incidence rates will also be provided as well as summaries. More details will be outlined in the SAP.

## 6.6 PATIENT-REPORTED OUTCOME ANALYSES

Patient-reported outcomes will include the Patient's Global Assessment of Disease Activity, and data from the HAQ-DI, RAID and WPAI:RA questionnaires. Details of the analysis methodology for these secondary endpoints will be provided in the SAP.

## 6.7 EXPLORATORY ANALYSES

An exploratory subgroup analysis of TCZ experienced and TCZ naïve patients will be performed. Other exploratory analyses will be described in the SAP.

## 6.8 INTERIM ANALYSES

### 6.8.1 Planned Interim Analyses

Interim analyses of safety, and potentially also efficacy data if requested by the iDMC to assess risk-benefit, will be conducted in the context of the periodic data reviews by the iDMC and further details will be provided in the iDMC charter. There are no statistical stopping rules based on efficacy or safety variables for this study.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of

discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

## 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

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 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, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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 7.5.

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 study site must also allow inspection by applicable health authorities.

### 7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study 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.

### 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, 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), with the E.U. Clinical Trial Directive (2001/20/EC), as well as applicable local laws.

### 8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. Patients who decline to participate will not provide a separate signature.

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.

## 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 9.6).

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 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 be disclosed to third parties only 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 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 1 year after completion of the study (i.e., the date of the last visit of the last participating patient in this study).

# 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, including an audit trail containing a complete record of all changes to data.

## 9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

## 9.3 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.

## 9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by Roche, who has overall responsibility for this study.

CROs will be responsible for medical monitoring, data management support, randomization (IxRS) and statistical analysis.

A Steering Committee will oversee the general conduct of the study.

An iDMC will share responsibility for evaluating the safety of the patients participating in the trial at regular intervals throughout the study.

## 9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. 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.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-centre trials only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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.

## 9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. 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 changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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# 11. APPENDICES

## APPENDIX 1: SCHEDULE OF ASSESSMENTS - SCREENING (ALL PATIENTS) & LEAD-IN PHASE (TRACK TCZ-NAÏVE)

| | ALL PATIENTS | *LEAD-IN: TRACK TCZ-NAÏVE* PATIENTS ONLY | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit name** | **Screening Visit [1,2]** | **LI V1** | **LI V2** | **IV TCZ ONLY LI Wk8** | **LI V3** | **IV TCZ ONLY LI Wk12** | **Pre-Rand** | **Pre-Rand (if extension)** |
| **Week** | TCZ Exp: Up to -6<br>TCZ Naïve: Up to LI -4 | **LI 1** | **LI 4** | **LI 8** | **LI 12** | **LI 16** | **LI 20** | **(LI 24)** |
| **Day** | TCZ Exp: Up to -42<br>TCZ Naïve: Up to LI -28 | **LI 1** | **LI 29** | **LI 56** | **LI 85** | **LI 113** | **LI 141** | **(LI 169)** |
| **Time window (days)** | | | **± 4** | **± 4** | **± 14 for SC<br>± 4 for IV** | **± 4** | **± 4** | **± 4** |
| Informed consent [3] | X | | | | | | | |
| Inclusion/exclusion criteria [4] | X | | | | | | | |
| Demographics and medical history [5] | X | | | | | | | |
| Complete physical examination [6] | X | | | | | | X | |
| **Conduct PROs prior to RA Evaluation & IMP administration:** | | | | | | | | |
| HAQ-DI; RAID; WPAI-RA [7] | | X | | | | | | |
| Patient Global VAS [7] | X | X | X | | X | | X | (X) |
| **RA Evaluation (Efficacy)** | | | | | | | | |
| 66/68 Joint Count [8] | | X | | | | | | |
| DAS28 Joint Count [9] | X | X | X | | X | | X | (X) |
| Physician Global VAS [10] | | X | X | | X | | X | |
| Morning Stiffness [11] | | X | X | | X | | X | |

| | ALL PATIENTS | *LEAD-IN: TRACK TCZ-NAÏVE* PATIENTS ONLY | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit name** | **Screening Visit [1,2]** | **LI V1** | **LI V2** | **IV TCZ ONLY LI Wk8** | **LI V3** | **IV TCZ ONLY LI Wk12** | **Pre-Rand** | **Pre-Rand (if extension)** |
| **Week** | TCZ Exp: Up to -6<br>TCZ Naïve: Up to LI -4 | **LI 1** | **LI 4** | **LI 8** | **LI 12** | **LI 16** | **LI 20** | **(LI 24)** |
| **Day** | TCZ Exp: Up to -42<br>TCZ Naïve: Up to LI -28 | **LI 1** | **LI 29** | **LI 56** | **LI 85** | **LI 113** | **LI 141** | **(LI 169)** |
| **Time window (days)** | | | **± 4** | **± 4** | **± 14 for SC<br>± 4 for IV** | **± 4** | **± 4** | **± 4** |
| DAS28 ESR Calculation [12] | X | X | X | | X | | X | (X) |
| **Safety and Other Assessments** | | | | | | | | |
| Vital signs [13] | X | X | X | | X | | X | (X) |
| Concomitant therapy [14] | X | X | X | X | X | X | X | (X) |
| Adverse events [15] | X | X | X | X | X | X | X | (X) |
| **Local Lab [16]** | | | | | | | | |
| ESR (Westergren, use central lab kit) | X | X | X | | X | | X | (X) |
| Pregnancy (Urine, use central lab kit) [17] | | X | X | X | X | X | X | (X) |
| Confirmatory Liver Function Test | | If LFT confirmation required. [18] | | | | | | |
| Tuberculosis Testing **(see note!) [19]**<br>Tuberculin Skin Test/PPD | X Not all patients (see note) | | | | | | | |
| **Central Lab [16] [20], FASTING** | | | | | | | | |
| C-peptide (serum, ambient & -20°C) | | X | | | | | | |
| Glucose (plasma, ambient) | | X | | | | | | |

| | ALL PATIENTS | *LEAD-IN: TRACK TCZ-NAÏVE* PATIENTS ONLY | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit name** | **Screening Visit [1,2]** | **LI V1** | **LI V2** | **IV TCZ ONLY LI Wk8** | **LI V3** | **IV TCZ ONLY LI Wk12** | **Pre-Rand** | **Pre-Rand (if extension)** |
| **Week** | TCZ Exp: Up to -6<br>TCZ Naïve: Up to LI -4 | **LI 1** | **LI 4** | **LI 8** | **LI 12** | **LI 16** | **LI 20** | **(LI 24)** |
| **Day** | TCZ Exp: Up to -42<br>TCZ Naïve: Up to LI -28 | **LI 1** | **LI 29** | **LI 56** | **LI 85** | **LI 113** | **LI 141** | **(LI 169)** |
| **Time window (days)** | | | **± 4** | **± 4** | **± 14 for SC<br>± 4 for IV** | **± 4** | **± 4** | **± 4** |
| HbA1c (whole blood, **-70°C**) | | X | | | | | | |
| Lipid Panel (serum, ambient) | X | X | X | | X | | X | |
| **Central Lab [16]** | | | | | | | | |
| Tuberculosis Testing **(see note!) [19]**<br>QuantiFERON (plasma, **-70°C**) | X Not all patients<br>(see note) | | | | | | | |
| RF, Anti-CCP Ab (serum, -20°C) [21] | X | | | | | | | |
| HBsAg, HBcAb, HCV Ab [22] | X | | | | | | | |
| Chemistry (serum, ambient) | X | X | X | | X | | X | |
| hsCRP (serum, ambient & -20°C) | | X | X | | X | | X | (X) |
| Hematology (whole blood, ambient) | X | X | X | | X | | X | |
| 25-OH Vitamin D (serum, -20°C) | | X | | | | | | |
| Bone turnover: P1NP (serum, -20°C) | X (TCZ Exp only) | | | | | | X | |
| Bone turnover: CTX-1 (serum, -20°C) | X (TCZ Exp only) | | | | | | X | |
| Urinalysis [urine, ambient] | X | | | | | | X | |

| | ALL PATIENTS | *LEAD-IN: TRACK TCZ-NAÏVE* PATIENTS ONLY | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit name** | **Screening Visit [1,2]** | **LI V1** | **LI V2** | **IV TCZ ONLY LI Wk8** | **LI V3** | **IV TCZ ONLY LI Wk12** | **Pre-Rand** | **Pre-Rand (if extension)** |
| **Week** | TCZ Exp: Up to -6<br>TCZ Naïve: Up to LI -4 | **LI 1** | **LI 4** | **LI 8** | **LI 12** | **LI 16** | **LI 20** | **(LI 24)** |
| **Day** | TCZ Exp: Up to -42<br>TCZ Naïve: Up to LI -28 | **LI 1** | **LI 29** | **LI 56** | **LI 85** | **LI 113** | **LI 141** | **(LI 169)** |
| **Time window (days)** | | | **± 4** | **± 4** | **± 14 for SC<br>± 4 for IV** | **± 4** | **± 4** | **± 4** |
| RNA (whole blood RNA Paxgene,-20°C) | | X | | | | | | |
| Exploratory biomarkers (serum, **-70°C**) | | X | | | | | | |
| **Central Lab: event-driven [16]** | | | | | | | | |
| Beta-HCG (serum, ambient) [17] | X | If urine pregnancy test is positive | | | | | | |
| Confirmatory Liver Function Test (serum, ambient) | No testing | If LFT confirmation required. [18] | | | | | | |
| Immunogenicity<br>• TCZ-IL-6SR & IL-6 (serum, -20°C)<br>• Anti-TCZ AB/HAHA (serum, **-70°C**) | X<br>Baseline | If anaphylaxis or other hypersensitivity reaction (serious or non-serious). Obtain sample at time of event and again at 8 weeks after the event. [23] | | | | | | |
| **IMP and Sponsor-Provided Open-Label (SP OL) Prednisone Dispensing** | | | | | | | | |
| Study TCZ (IMP) | No drug | X | X | X | X | X | X | X |
| TCZ-Naïve: SP OL Prednisone [24] | No drug | | | | | | X [24] | (X) |
| TCZ-Experienced: SP OL Prednisone [24] | X | | | | | | | |

**Lead-in Phase only: the next scheduled visit is cancelled for patients who permanently and prematurely discontinue IMP (TCZ SC or TCZ IV). These patients must then attend the visits listed in Appendix 3.**

1. **Track TCZ-experienced patients only:** The Screening Visit must occur up to 6 weeks prior to Randomization. The Randomization Visit is shown in Appendix 2.
2. **Track TCZ-naïve patients only:** candidate patients may have their initial Screening Visit up to 4 weeks prior to enrolment in the Lead-in Phase. Lead-in Visit 1 is shown in this Appendix.
3. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations (Section 4.5.1).
4. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria (see Section 4.1) before entering the study. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
5. Demographic data and medical history will be collected as per Section 4.5.2.
6. Complete physical examination will be performed as per Section 4.5.3.
7. Patient Reported Outcomes: see Appendix 4, Appendix 5, Appendix 6, and Appendix 10.

**RA Evaluation (Efficacy)**

8. Joints are assessed for swelling (66 joints) and tenderness (68 joints) as per Appendix 8.
9. 28 joints are assessed for swelling and tenderness for calculating the DAS 28. See Appendix 8.
10. Physician Global VAS: see Appendix 10.
11. Morning Stiffness: see Section 4.5.8.4
12. DAS28 ESR Calculation: **the eCRF will automatically calculate the DAS28 ESR. However, in case the related data are not entered into the eCRF during the visit, the investigator will have to calculate the DAS28 ESR manually for purposes of medical decision making, including to assess whether or not the patient has a flare which requires treatment.** See Section 4.5.8.3 **for further details**.

**Safety and Other Assessments**

13. Vital signs: temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position. *Screening, LI Week 20 and Week 24 post randomization only: body weight and body mass index (BMI) (Height collected at screening only).* (Section 4.5.4.)

14. Concomitant Therapy includes all medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient (Section 4.5.5).
15. Adverse events must be collected and reported as per Section 5. Please note:
    - After informed consent has been obtained but prior to the initiation of treatment in the Tapering Phase, only SAEs caused by a protocol-mandated intervention should be reported.
    - After the initiation of treatment in the Tapering Phase, all AEs will be reported until 4 weeks after the last dose of TCZ / study prednisone. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.
    - The investigator should follow each AE 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 SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

**Laboratory (Local and Central)**

16. Please refer to the **Central Laboratory Services Manual** [redacted] for instructions regarding all laboratory tests (including those to be performed locally using kits provided by the Central Laboratory). All laboratory assessments are described in Section 4.5.6.
17. **All women who are not post-menopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile are subject to pregnancy testing (i.e., Beta-HCG urine and serum). Serum Beta-HCG is conducted at baseline for all patients.**
18. The patient may need **confirmatory liver function testing** in the event of an elevated liver function test finding which may lead to study drug discontinuation, as described in Section 4.6.2 and Section 5.1.1.7. The first sample should be sent to the local laboratory to facilitate rapid clinical decision making. Another second sample (collected at the same time as the first sample) should be sent to the Central laboratory.
19. Tuberculosis Testing instructions apply as per Appendix 9. All *Track TCZ-naïve* patients and some *Track TCZ-experienced* patients will require either a tuberculosis skin test (conducted at the site without kit provided by Central Lab) or a QuantiFERON (sent to the Central Laboratory and **special handling applies.** Refer to the Central Laboratory Services Manual ([redacted]. Investigators should take into consideration the time required to obtain the results of these tests.
20. Patient should fast for 12 hours prior to the test. The patient may drink only water. Tea, coffee, diet drinks, or other beverages are not allowed. The patient should not smoke, chew gum, or exercise during this time. Study medications are allowed only if scheduled. Other medications are allowed or prohibited during fasting as per investigator judgment.
21. Rheumatoid factor (e.g. latex test), anti-cyclic citrullinated peptide antibody
22. Hepatitis B surface antigen, hepatitis B core antibody and hepatitis C virus antibodies will only be tested if clinical suspicion based on history or clinical evidence of exposure (Section 4.5.6).

23. Immunogenicity sampling will be conducted for all patients during screening. Subsequent sampling is "event-driven" in patients who experience anaphylaxis or other hypersensitivity reaction (serious or non-serious). Sampling is conducted at the time of the event and again at 8 weeks after the event. The instructions in the **Central Laboratory Services Manual** [redacted] must be followed.
24. ***Track TCZ-naïve* patients only:** The instructions for mandatory switching to Sponsor provide open-label (SP-OL) prednisone are in Section 4.3.2.2. Patients who granted an extension will only be switched to SP-OL prednisone at Lead-in Week 24 if they meet the criteria specified in Section 4.3.2.2.
    ***Track TCZ-experienced* patients only:** Patients who have signed informed consent and are on prednisone 5 mg/day (or GC equivalent) at the Screening Visit are immediately switched to SP-OL prednisone, as per Section 4.3.2.2.

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## APPENDIX 2: SCHEDULE OF ASSESSMENTS - 24 WEEK TAPERING PHASE (ALL PATIENTS)

| ALL RANDOMIZED PATIENTS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Visit name** | **V1** | **V2** | **V3** | **V4** | **V5** | **IV TCZ ONLY** | **V6 EOT** | **Safety F/U EOS** | **Flare Assess.** |
| **Week** | **1** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | |
| **Day** | **1** | **29** | **57** | **85** | **113** | **141** | **169** | **197** | **Flare +14d** |
| **Time window (days)** | | **± 4** | **± 4** | **± 4** | **± 4** | **± 4** | **± 4** | **± 4** | **± 2** |
| Randomization [1] | X | | | | | | | | |
| **Conduct PROs prior to RA Evaluation & IMP administration:** | | | | | | | | | |
| HAQ-DI; RAID; WPAI-RA [2] | X | | | | | | X | | |
| Patient Global VAS [2] | X | X | X | X | X | | X | X | X |
| **RA Evaluation (Efficacy)** | | | | | | | | | |
| 66/68 & DAS28 Joint Count [3] | X | X | X | X | X | | X | | X |
| Physician Global VAS [4] | X | X | X | X | X | | X | | X |
| Morning Stiffness [5] | X | X | X | X | X | | X | | X |
| DAS28 ESR Calculation [6] | X | X | X | X | X | | X | | X |
| **Safety and Other Assessments** | | | | | | | | | |
| Vital signs [7] | X | X | X | X | X | | X | X | X |
| Concomitant therapy [8] | X | X | X | X | X | X | X | X | X |
| Adverse events [9] | X | X | X | X | X | X | X | X | X |
| **Local Lab [10]** | | | | | | | | | |
| ESR (Westergren, use central lab kit) | X | X | X | X | X | | X | | X |
| Pregnancy (Urine, use central lab kit) [11] | X | X | X | X | X | X | X | X | |
| Confirmatory Liver Function Test | Event driven: if LFT confirmation required. [12] | | | | | | | | |
| **Central Lab [10] [13], FASTING** | | | | | | | | | |
| C-peptide (serum, ambient & -20°C) | X | | | X | | | X | | |
| Glucose (plasma, ambient) | X | | | X | | | X | | |
| HbA1c (whole blood, **-70°C**) | X | | | X | | | X | | |
| Lipid Panel (serum, ambient) | X | X | | X | | | X | | |
| **Central Lab [10]** | | | | | | | | | |
| Chemistry (serum, ambient) | X | X | X | X | X | | X | | |
| hsCRP (serum, ambient & -20°C) | X | X | X | X | X | | X | | X |

| ALL RANDOMIZED PATIENTS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Visit name** | **V1** | **V2** | **V3** | **V4** | **V5** | **IV TCZ ONLY** | **V6 EOT** | **Safety F/U EOS** | **Flare Assess.** |
| **Week** | **1** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | |
| **Day** | **1** | **29** | **57** | **85** | **113** | **141** | **169** | **197** | **Flare +14d** |
| **Time window (days)** | | **± 4** | **± 4** | **± 4** | **± 4** | **± 4** | **± 4** | **± 4** | **± 2** |
| Hematology (whole blood, ambient) | X | X | X | X | X | | X | | |
| 25-OH Vitamin D (serum, -20°C) | X | | | | | | | | |
| Bone turnover: P1NP (serum, -20°C) | X | | | | | | X | | |
| Bone turnover: CTX-1 (serum, -20°C) | X | | | | | | X | | |
| RNA (whole blood RNA Paxgene, -20°C) | X | | X | | | | X | | |
| Exploratory biomarkers (serum, **-70°C**) | X | | X | | | | X | | |
| **Central Lab: special RBR consent required [14] [10]** | | | | | | | | | |
| DNA (whole blood, **-70°C**) | X | | | | | | | | |
| **Central Lab: event-driven [10]** | | | | | | | | | |
| Beta-HCG (serum, ambient) [11] | | If urine pregnancy test is positive | | | | | | | |
| Confirmatory Liver Function Test (serum, ambient) | | If LFT confirmation required. [12] | | | | | | | |
| Immunogenicity<br>• TCZ-IL-6SR & IL-6 (serum, -20°C)<br>• Anti-TCZ AB/HAHA (serum, **-70°C**) | | If anaphylaxis or other hypersensitivity reaction (serious or non-serious). Obtain sample at time of event and again at 8 weeks after the event. [15]. | | | | | | | |
| **IMP and Flare Drug Dispensing** | | | | | | | | | |
| Study TCZ (IMP) | X | X | X | X | X | X | | | |
| Study prednisone (IMP) | X | X | X | X | X | X | | | |
| Flare Rescue Medication (Sponsor provided open-label prednisone) | If RA flare.<br>**Important instructions apply!** [16] | | | | | | | | |

**The next scheduled visit is cancelled for patients who permanently and prematurely discontinue IMP (either TCZ SC/IV or study prednisone). These patients must then attend the visits listed in Appendix 3.**

1. The randomization criteria (as per Section 4.5.10) must be reviewed to confirm eligibility before the patient is randomized. The investigator will maintain a log of all patients entered into the study but not randomized, including the reasons for not randomization, as applicable.
2. Patient Reported Outcomes: see Appendix 4, Appendix 5, Appendix 6, and Appendix 10.

**RA Evaluation**

3. Joints are assessed for tenderness (68 joints) and swelling (66 joints). Of these, 28 joints are simultaneously assessed for DAS 28 calculation. See Appendix 8.
4. Physician Global VAS: see Appendix 10.
5. Morning Stiffness: see Section 4.5.8.4
6. DAS28 ESR Calculation: the eCRF will automatically calculate the DAS28 ESR. However, in case the related data are not entered into the eCRF during the visit, the investigator will have to calculate the DAS28 ESR manually for purposes of medical decision making, including to assess whether or not the patient has a RA flare which requires treatment. See Section 4.5.8.3 for further details.

**Other Assessments**

7. Vital signs: temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position. *Screening, LI Week 20 and Week 24 post randomization only:* body weight and body mass index (BMI) (Height collected at screening only). (Section 4.5.4.)
8. Concomitant Therapy includes all medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient (Section 4.5.5).
9. Adverse events must be collected and reported as per Section 5. Please note:

- After informed consent has been obtained but prior to the initiation of treatment in the Tapering Phase, only SAEs caused by a protocol-mandated intervention should be reported.
- After the initiation of treatment in the Tapering Phase, all AEs will be reported until 4 weeks after the last dose of TCZ / study prednisone. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.
- The investigator should follow each AE 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 SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

**Laboratory (Local and Central)**

10. Please refer to the **Central Laboratory Services Manual** [redacted] for instructions regarding all laboratory tests (including those to be performed locally using kits provided by the Central Laboratory). All laboratory assessments are described in Section 4.5.6.
11. All women who are not post-menopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile are subject to pregnancy testing (i.e., Beta-HCG urine and serum).
12. The patient may need **confirmatory liver function testing** in the event of an elevated liver function test finding which may lead to study drug discontinuation, as described in Section 4.6.2 and Section 5.1.1.7. The first sample should be sent to the local laboratory to facilitate rapid clinical decision making. Another second sample (collected at the same time as the first sample) should be sent to the Central laboratory.
13. Patient should fast for 12 hours prior to the test. The patient may drink only water. Tea, coffee, diet drinks, or other beverages are not allowed. The patient should not smoke, chew gum, or exercise during this time. Study medications are allowed only if scheduled. Other medications are allowed or prohibited during fasting as per investigator judgment.

14. DNA samples may be drawn only if the site has been granted approval for RBR sampling and if the patient has given specific consent to participate in this optional research (see Section 4.5.12).
15. Immunogenicity sampling is "event-driven" in patients who experience anaphylaxis or other hypersensitivity reaction (serious or non-serious). Sampling is conducted at the time of the event and again at 8 weeks after the event. The instructions in the **Central Laboratory Services Manual** [redacted] must be followed. No immunogenicity sampling is required in case of injection site reactions.
16. Patients must be treated with RA flare rescue medication and attend a Flare Assessment visit if a RA flare is detected at any scheduled or unscheduled visit. Important instructions apply, see Section 4.5.11.

## APPENDIX 3: SCHEDULE OF ASSESSMENTS - EARLY TREATMENT DISCONTINUATIONS

Any patient who permanently and prematurely discontinues IMP (TCZ SC or study prednisone) during the Lead-in Phase or Tapering Phase will attend a **Study Treatment Discontinuation Visit**, followed in 4 weeks by a **Safety Monitoring Visit**. Randomized patients are also encouraged to attend a **Limited Week 24 Assessment Visit** at 24 Weeks post-randomization.

- The Safety Monitoring Visit is waived for randomized patients attending the Limited Week 24 Assessment Visit within 4 weeks of the Study Treatment Discontinuation Visit.
- The Study Treatment Discontinuation Visit is waived for randomized patients who discontinue study treatment within 2 weeks after randomization. These patients must attend the Safety Monitoring Visit 4 weeks after their last dose.

Any patient who prematurely discontinues study medication will be subsequently treated according to local clinical practice at the discretion of the investigator.

| ALL DISCONTINUED STUDY PATIENTS (LEAD-IN PHASE AND TAPERING PHASE) | | | |
|---|---|---|---|
| Visit name | Study Treatment Discontinuation | Limited Week 24 Assessment | Safety Monitoring |
| Week | | Week 24 | 4 Weeks after Treatment D/C |
| Day | At the time of Treatment D/C | Day 169 | |
| Time window (days) | | ± 4 days | ± 4 days |
| **Conduct PROs prior to RA Evaluation & IMP administration:** HAQ-DI ; Patient Global VAS [1] | X | X | |
| **RA Evaluation (Efficacy)** | | | |
| 66/68 & DAS28 Joint Count [2] | X | X | |
| Physician Global VAS [3] | X | X | |
| Morning Stiffness [4] | X | X | |
| DAS28 ESR Calculation [5] | X | X | |
| **Safety and Other Assessments** | | | |
| Vital signs [6] | X | X | X |
| Concomitant therapy [7] | X | X | X |
| Adverse events [8] | X | X | X |
| **Local Lab [9]** | | | |

| ALL DISCONTINUED STUDY PATIENTS (LEAD-IN PHASE AND TAPERING PHASE) | | | |
|---|---|---|---|
| Visit name | Study Treatment Discontinuation | Limited Week 24 Assessment | Safety Monitoring |
| Week | | Week 24 | 4 Weeks after Treatment D/C |
| Day | At the time of Treatment D/C | Day 169 | |
| Time window (days) | | ± 4 days | ± 4 days |
| ESR (Westergren, use central lab kit) | X | X | |
| Pregnancy (Urine, use central lab kit) [10] | X | X | X |
| Confirmatory Liver Function Test | If LFT confirmation required. [11] | | |
| **Central Lab [9] [12], FASTING** | | | |
| C-peptide (serum, ambient & -20°C) | X | | |
| Glucose (plasma, ambient) | X | | |
| HbA1c (whole blood, **-70°C**) | X | | |
| Lipid Panel (serum, ambient) | X | | |
| **Central Lab [9]** | | | |
| Chemistry (serum, ambient) | X | | |
| hsCRP (serum, ambient & -20°C) | X | | |
| Haematology (whole blood, ambient) | X | | |
| RNA (whole blood RNA Paxgene, -20°C) | X | | |
| Exploratory biomarkers (serum, **-70°C**) | X | | |
| **Central Lab: event-driven [9]** | | | |
| Beta-HCG (serum, ambient) [10] | If urine pregnancy test is positive | | |
| Confirmatory Liver Function Test (serum, ambient) | If LFT confirmation required. [11] | | |
| Immunogenicity<br>• TCZ-IL-6SR & IL-6 (serum, -20°C)<br>• Anti-TCZ AB/HAHA (serum, **-70°C**) | If anaphylaxis or other hypersensitivity reaction (serious or non-serious). Obtain sample at time of event and again at 8 weeks after the event. [13]. | | |

1. Patient Reported Outcomes: see Appendix 4, Appendix 5, Appendix 6, and Appendix 10.

**RA Evaluation**

2. Joints are assessed for tenderness (68 joints) and swelling (66 joints). Of these, 28 joints are simultaneously assessed for DAS 28 calculation. See Appendix 8.
3. Physician Global VAS: see Appendix 10.
4. Morning Stiffness: see Section 4.5.8.4

5. DAS28 ESR Calculation: the eCRF will automatically calculate the DAS28 ESR. However, in case the related data are not entered into the eCRF during the visit, the investigator will have to calculate the DAS28 ESR manually for purposes of medical decision making, including to assess whether or not the patient has a RA flare which requires treatment. See Section 4.5.8.3 for further details.

**Other Assessments**

6. Vital signs: temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position. *Study Treatment D/C Visit only: body weight and body mass index (BMI) (Height collected at screening only).* (Section 4.5.4.)
7. Concomitant Therapy includes all medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient (Section 4.5.5).
8. Adverse events must be collected and reported as per Section 5. Please note:
   - All AEs will be reported until 4 weeks after the last dose of TCZ / study prednisone.
   - After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.
   - The investigator should follow each AE 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 SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

**Laboratory (Local and Central)**

9. Please refer to the **Central Laboratory Services Manual (**[redacted]**)** for instructions regarding all laboratory tests (including those to be performed locally using kits provided by the Central Laboratory). All laboratory assessments are described in Section 4.5.6.
10. **All women who are not post-menopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile are subject to pregnancy testing (i.e., Beta-HCG urine and serum).**
11. The patient may need **confirmatory liver function testing** in the event of an elevated liver function test finding which may lead to study drug discontinuation, as described in Section 4.6.2 and Section 5.1.1.7. The first sample should be sent to the local laboratory to facilitate rapid clinical decision making. Another second sample (collected at the same time as the first sample) should be sent to the Central laboratory.
12. Patient should fast for 12 hours prior to the test. The patient may drink only water. Tea, coffee, diet drinks, or other beverages are not allowed. The patient should not smoke, chew gum, or exercise during this time. Study medications are allowed only if scheduled. Other medications are allowed or prohibited during fasting as per investigator judgment.
13. Immunogenicity sampling is "event-driven" in patients who experience anaphylaxis or other hypersensitivity reaction (serious or non-serious). Sampling is conducted at the time of the event and again at 8 weeks after the event. The instructions in the **Central Laboratory Services Manual** [redacted] must be followed. No immunogenicity sampling is required in case of injection site reactions.

## APPENDIX 4: HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)

CTRN # _____ → Patient # _____ → Visit # _____ → MA29585 – SEMIRA

### HEALTH ASSESSMENT QUESTIONNAIRE

PATKEY# →
QUESTDAT →

**Name** _____ → _____ → **Date** _____ → _____

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

HAQADMIN →

**Please tick the response that best describes your usual abilities OVER THE PAST WEEK:**

QUESTYPE →

PMSVIS →
RASTUDY →
QUESTNUM →

| | Without ANY Difficulty | With SOME Difficulty | With MUCH Difficulty | UNABLE To Do | |
|---|---|---|---|---|---|
| **DRESSING & GROOMING** | | | | | |
| Are you able to: | | | | | |
| →Dress yourself, including tying shoelaces and doing up buttons? | _____ | _____ | _____ | _____ | |
| →Wash your hair? | _____ | _____ | _____ | _____ | DRESSNEW → |
| **GETTING UP** | | | | | |
| Are you able to: | | | | | |
| →Stand up from a straight-backed chair? | _____ | _____ | _____ | _____ | |
| →Get in and out of bed? | _____ | _____ | _____ | _____ | RISENEW → |
| **EATING** | | | | | |
| Are you able to: | | | | | |
| →Cut up your meat? | _____ | _____ | _____ | _____ | |
| →Lift a full cup or glass to your mouth? | _____ | _____ | _____ | _____ | |
| →Open a cereal packet? | _____ | _____ | _____ | _____ | EATNEW → |
| **WALKING** | | | | | |
| Are you able to: | | | | | |
| →Walk outdoors on flat ground? | _____ | _____ | _____ | _____ | |
| →Climb up five steps? | _____ | _____ | _____ | _____ | WALKNEW → |

**Please tick any of the following AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:**

_____ Walking stick
_____ Walking frame
_____ Crutches
_____ Wheelchair
_____ Aids used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Specially adapted utensils (such as for eating and cooking)
_____ Specially adapted chair
_____ Other (Please specify: _____)

DRSGASST →
RISEASST →

**Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:**

_____ Dressing and Grooming
_____ Getting up
_____ Eating
_____ Walking

EATASST →
WALKASST →



HAQ-DI - United Kingdom/English - 03 July 2009 - Mapi
ID5240 / HAQ-DI_AU1.0_eng-GB2.doc

**Please tick the response that best describes your usual abilities OVER THE PAST WEEK:**

| | Without ANY Difficulty | With SOME Difficulty | With MUCH Difficulty | UNABLE To Do | |
|---|---|---|---|---|---|
| **HYGIENE** | | | | | |
| Are you able to: | | | | | |
| →Wash and dry your body? | _____ | _____ | _____ | _____ | |
| →Have a bath? | _____ | _____ | _____ | _____ | |
| →Get on and off the toilet? | _____ | _____ | _____ | _____ | HYGNNEW → |
| **REACH** | | | | | |
| Are you able to: | | | | | |
| →Reach up for and take down a 5 lb object (e.g. a bag of potatoes) from just above your head? | _____ | _____ | _____ | _____ | |
| →Bend down to pick up clothing from the floor? | _____ | _____ | _____ | _____ | REACHNEW → |
| **GRIP** | | | | | |
| Are you able to: | | | | | |
| →Open car doors? | _____ | _____ | _____ | _____ | |
| →Open jars which have been previously opened? | _____ | _____ | _____ | _____ | |
| →Turn taps on and off? | _____ | _____ | _____ | _____ | GRIPNEW → |
| **ACTIVITIES** | | | | | |
| Are you able to: | | | | | |
| →Go shopping? | _____ | _____ | _____ | _____ | |
| →Get in and out of a car? | _____ | _____ | _____ | _____ | |
| →Do chores such as vacuuming or gardening? | _____ | _____ | _____ | _____ | ACTIVNEW → |

**Please tick any of the following AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:**

_____ Raised toilet seat
_____ Bath seat
_____ Jar opener (for jars previously opened)
_____ Bath rail
_____ Long-handled appliances for reaching things
_____ Long-handled appliances in bathroom (e.g. a long-handled brush.
_____ Other (Please specify: _____)

**Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:** HYGNASST →

_____ Hygiene
_____ Reaching
_____ Gripping and opening things
_____ Shopping and housework

RCHASST →
GRIPASST →
ACTVASST →

We are also interested in learning whether or not you are affected by pain because of your illness.

**How much pain have you had because of your illness IN THE PAST WEEK:**

INDICATE THE SEVERITY OF THE PAIN BY PLACING A VERTICAL (I) BAR ON THE LINE

NO PAIN 0 ——————————————— SEVERE PAIN 100 PAINSCAL →

## APPENDIX 5: RHEUMATOID ARTHRITIS IMPACT OF DISEASE (RAID) QUESTIONNAIRE

**1. Pain**

Circle the number that best describes the pain you felt due to your rheumatoid arthritis during the last 7 days:

| None | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

**2. Functional disability assessment**

Circle the number that best describes the difficulty you had in doing daily physical activities due to your rheumatoid arthritis during the last 7 days.

| No difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

**3. Fatigue**

Circle the number that best describes how much fatigue you felt due to your rheumatoid arthritis during the last 7 days.

| No fatigue | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Totally exhausted |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

**4. Sleep**

Circle the number that best describes the sleep difficulties (i.e., resting at night) you felt due to your rheumatoid arthritis during the last 7 days.

| No difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

**5. Physical well-being**

Considering your arthritis overall, how would you rate your level of physical well-being during the last 7 days ?

Circle the number that best describes your level of physical well-being.

| Very good | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very bad |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

**6. Emotional well-being**

Considering your arthritis overall, how would you rate your level of emotional well-being during the last 7 days? Circle the number that best describes your level of emotional well-being.

| Very good | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very bad |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

**7. Coping**

Considering your arthritis overall, how well did you cope (manage, deal, make do) with your disease during the last 7 days?

| Very well | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very poorly |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

**RAID SCORING AND CALCULATION RULES**

The RAID is calculated based on 7 Numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10. The 7 NRS correspond to pain, function, fatigue, sleep, emotional well-being, physical well-being, and coping/self-efficacy.

**1. CALCULATION**

**Pain** NRS value (range 0-10) x 0.21 +

**Function** NRS value (range 0-10) x 0.16 +

**Fatigue** NRS value (range 0-10) x 0.15 +

**Physical well-being** NRS value (range 0-10) x 0.12 +

**Sleep** NRS value (range 0-10) x 0.12 +

**Emotional well-being** NRS value (range 0-10) x 0.12 +

**Coping** NRS value (range 0-10) x 0.12 =

---

**RAID final value**

*The range of the final RAID value is 0-10 where higher figures indicate worse status.*

**2. MISSING DATA IMPUTATION**

- If **one** of the 7 NRS values composing the RAID is missing, the imputation is as follows:
    a. calculate the mean value of the 6 other (non-missing) NRS (range, 0-10)
    b. impute this value for the missing NRS
    c. then, calculate the RAID as explained above.
- If **two or more** of the NRS values are missing, the RAID is considered as missing value (no imputation).

## APPENDIX 6: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE RHEUMATOID ARTHRITIS ENGLISH-US V2.0 (WPAI:RA)

The following questions ask about the effect of your rheumatoid arthritis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   *If NO, check "NO" and skip to question 6.*

The next questions are about the **past seven days**, not including today.

*2.* During the past seven days, how many hours did you miss from work because of problems associated with your rheumatoid arthritis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your rheumatoid arthritis. Do not include time you missed to participate in this study.*

_____ HOURS

*3.* During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

*4.* During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6.)*

*5.* During the past seven days, how much did your rheumatoid arthritis affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If rheumatoid arthritis affected your work only a little, choose a low number. Choose a high number if rheumatoid arthritis affected your work a great deal.

Consider only how much rheumatoid arthritis affected productivity while you were working.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rheumatoid arthritis had no effect on my work | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Rheumatoid arthritis completely prevented me from working |

CIRCLE A NUMBER

*6.* During the past seven days, how much did your rheumatoid arthritis affect your ability o do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If rheumatoid arthritis affected your activities only a little, choose a low number. Choose a high number if rheumatoid arthritis affected your activities a great deal.*

Consider only how much rheumatoid arthritis affected your ability to do your regular daily activities, other than work at a job.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rheumatoid arthritis had no effect on my daily activities | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Rheumatoid arthritis completely prevented me from doing my daily activities |

CIRCLE A NUMBER

WPAI:RA V2.0 (US English)

## APPENDIX 7: ACR REVISED CRITERIA FOR THE CLASSIFICATION OF FUNCTIONAL CAPACITY IN RHEUMATOID ARTHRITIS

**Class I**

Complete functional capacity with ability to carry on all usual duties without handicaps.

**Class II**

Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints.

**Class III**

Functional capacity adequate to perform only few or none of the duties of usual occupation or self-care.

**Class IV**

Largely or wholly incapacitated with subject bedridden or confined to wheel chair, permitting little or no self-care.

## APPENDIX 8: JOINTS TO BE ASSESSED FOR SWELLING AND TENDERNESS

### 66/68 JOINT COUNT

The joints assessed for the 66/68 are listed in the table below.

### DAS 28 JOINT COUNT

The 28 joints used to calculate DAS28 joint counts are indicated with: (DAS28).

| Joints to be assessed | Swelling (66) | Tenderness (68) |
|---|---|---|
| Temporomandibular joints | X | X |
| Sternoclavicular joints | X | X |
| Acromioclavicular joints | X | X |
| Shoulder joints | X (DAS 28) | X (DAS 28) |
| Elbow joints | X (DAS 28) | X (DAS 28) |
| Wrist joints | X (DAS 28) | X (DAS 28) |
| Interphalangeal on digit 1 | X (DAS 28) | X (DAS 28) |
| Distal interphalangeal on digits 2-5 | X | X |
| Proximal interphalangeal on digits 2-5 | X (DAS 28) | X (DAS 28) |
| Metacarpophalangeal on digits 1-5 | X (DAS 28) | X (DAS 28) |
| Hips | | X |
| Knees | X (DAS 28) | X (DAS 28) |
| Ankles | X | X |
| Tarsus | X | X |
| Interphalangeal on toes 1-5 | X | X |
| Metatarsophalangeal on toes 1-5 | X | X |

## APPENDIX 9: TUBERCULOSIS EVALUATION DURING SCREENING

### General Guidance

Benefit-risk in patient with current or history of active or latent TB

The benefit–risk balance of study-drug therapy should account for the fact that some patients previously treated for latent or active TB have developed active TB while being treated with tocilizumab. The potential risk of re-infection should be evaluated.

Priority of country-specific guidelines

Local country-specific guidelines must be followed for screening, test selection, test interpretation, diagnosis, and treatment of active and latent TB.

If no local guidelines exist for treatment of immunocompromised individuals, then the U.S. guidelines (located at: http://www.cdc.gov/tb/) must be followed.

Patient counselling

All patients should be instructed to seek medical advice if signs or symptoms (e.g., persistent cough, wasting/weight loss, low-grade fever) suggestive of TB occur during or after therapy with study drug.

#### 1. Tuberculosis Evaluation: Initial Assessment

All patients must receive a complete physical examination, medical history and concomitant medications assessment as per the Schedule of Assessments after signing informed consent. Based on these assessments, the investigator may exempt only the following patients from TB evaluation (TB; *Mycobacterium tuberculosis* infection):

- *Track-TCZ experienced* patients for whom there is no clinical suspicion of latent or active TB (e.g. no signs and symptoms of TB, no history of exposure or infection);
- Any patient already receiving antibiotic therapy for previously diagnosed latent TB at the time of signing informed consent and for whom there is no clinical suspicion of active TB. **Important note:** these patients must have completed $\geqslant$ 4 weeks antibiotic therapy prior to Enrolment. Antibiotic therapy should continue during screening and the study (if patient enrolled) as per local guidelines.

All other patients must undergo additional TB evaluation (items 2-4), as described below.

#### 2. Tuberculosis Evaluation: TST and IGRA

All patients selected for additional TB evaluation must receive one of the following tests during the study screening window:

- tuberculin skin test (TST), or
- interferon gamma releasing assay (IGRA) (Central Laboratory)

The choice of test must be based on local guidelines; however, investigators should note:

- An IGRA is typically preferred in patients with history of bacille Calmette Guérin vaccination (BCG vaccine).
- There is a risk of false-negative TST results due to immunosuppression, natural waning of immunity, and technical limitations (including reader variability)
- IGRA sensitivity is diminished by HIV infection and active TB.

**3. Tuberculosis Evaluation: Other Tests**

Additional assessments to confirm/exclude active and latent TB, if appropriate, should be conducted according to local guidelines during the study screening window. *It is the investigator's responsibility to be familiar with local TB testing guidelines and practices and to determine the need for additional testing.*

- Chest x-ray;
- Bacteriologic or histologic examinations (e.g. AFB smear, AFB cultures);
- Other tests (e.g. MRI, TB nucleic acid amplification test, NAAT).

**The results of all tests performed for purposes of TB evaluation must be available prior to the end of the screening window. Investigators should take into account the time required to obtain results for TSTs and IGRAs. IGRA results are available a few days after the Central Laboratory receives the blood sample; attention must be paid to special sample handling. TSTs are performed locally and require a patient follow up visit at 48 to 72 hours following administration.**

**4. Tuberculosis Evaluation: Diagnosis and Treatment**

All patients in whom active or latent TB has been excluded may enrol in the study if all other inclusion and no exclusion criteria are met.

All patients diagnosed with active or latent TB must be treated in accordance with local guidelines and a physician with expertise in the treatment of TB should be consulted. Furthermore, the following apply:

<u>All patients diagnosed with active TB during screening may not enrol in the study</u>

See exclusion criterion № 27

<u>*Track TCZ-naïve* patients diagnosed with latent TB during screening</u>

Patients are eligible for enrolment in the Lead-in Phase after completing ≥ 4 weeks treatment and meeting all inclusion and exclusion criteria at re-screening.

<u>Track TCZ-experienced patients diagnosed with latent TB during screening</u>

Patients are eligible for enrolment only if the following conditions are true:

- TCZ was interrupted at the time of initiation of latent TB antibiotic therapy;
- TCZ was restarted after completing ≥ 4 weeks of latent TB treatment;
- All inclusion and exclusion criteria are met at re-screening;
- Randomization criteria are met at the randomization visit.

## APPENDIX 10: GLOBAL ASSESSMENT OF DISEASE ACTIVITY VAS

The overall assessment of current disease activity will be made on a 100 mm horizontal visual analogue scale (VAS).

### Patient Global VAS

The patient should complete this assessment prior to the performance of all efficacy assessments and the administration of study treatment.

No Arthritis Symptoms ——————————————— Maximum Arthritis Symptoms

### Physician Global VAS

The investigator should complete this assessment prior to administration of study treatment.

No Arthritis Disease Activity ——————————————— Maximum Arthritis Disease Activity

## APPENDIX 11: RECOMMENDATIONS FOR MANAGEMENT OF ADRENAL INSUFFICIENCY

Management of potential adrenal insufficiency in study patients will be at the investigator's discretion. Use of the following recommendations is optional.

| | |
|---|---|
| **Clinical suspicion of adrenal insufficiency** | |
| **Check for cluster of typical symptoms** [1,2,3,4,5,6, ‡] | • Nausea, vomiting and diarrhoea<br>• Chronic fatigue and weakness<br>• Unexplained weight loss |
| **Check for characteristic physical signs** [4,6,7,8,9,10, ‡] | • Alabaster, pale-coloured skin<br>• Hypotension: Criteria: < 100 mmHg systolic and/or < 50 mmHg diastolic blood pressure<br>• Diffuse myalgia and arthralgia |
| **Conduct laboratory tests for clinical chemistry and biological parameters** | |
| **Check for alterations in clinical chemistry and biological parameters** [4,5,6,8,9,10, ‡] | • Hyponatraemia (criteria: < 135 mmol/l)<br>• Eosinophilia (criteria: > 0.5 G/l)<br>• Hypoglycaemia (criteria: glucose < 70 mg/dl)<br>• Hyperkalaemia (criteria: > 5 mEq/L)<br>• Metabolic acidosis (criteria: pH < 7.35) |
| **Confirmatory short ACTH stimulation test** | |
| **Conduct high-dose (250 µg) ACTH (cosyntropin) stimulation test** [2,4,7,10,11,12, ‡] | • Blood samples for serum cortisol are taken at 0, 30 and 60 minutes<br>  • An increase in serum cortisol level 30 or 60 minutes to above 500 nmol/L after the synthetic ACTH injection is considered a normal response Peak cortisol is < 400 nmol/l in most patients with secondary adrenal insufficiency after a short ACTH stimulation test |
| **Treatment according to investigator's discretion<br>Further tests as required and long-term clinical follow-up<br>Provide detailed patient education** | |
| **Glucocorticoid replacement Recommendation** [7,13, ‡] | • For patients with an acute symptomatic condition normally associated with a physiological increase in glucocorticoid output (e.g., febrile illness, certain procedures including colonoscopy and tooth extraction), additional hydrocortisone coverage should be considered over the period of the increased stress exposure. A suggested dose is hydrocortisone 60 mg/day provided as two or three doses with |

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| | half to two-thirds of the total dose given in the morning (immediately after rising from bed); for example, hydrocortisone 40 – 20 – 0 mg over the course of a day.<br>• For patients developing mild symptoms of adrenal insufficiency suspected to be due to tapering, prednisone should be increased by 1 mg / day, and the patient's symptoms re-assessed.<br>• Monitoring: history of glucocorticoid dose adjustment and potential adverse events, including any crisis since last visit, body weight, signs and symptoms suggestive of over-replacement or under-replacement, and ability to cope with daily stress (optional, fasting glucose) |
| **Management and prevention of adrenal crisis** [14, ‡] | • Patients with adrenal insufficiency are at risk of life-threatening adrenal crises. The major clinical features of adrenal crisis are hypotension and volume depletion. Under-dosing of glucocorticoids in an adrenal crisis is potentially hazardous. Adrenal crisis is best prevented by patient education and increasing the glucocorticoid dosage in situations of stressors known to increase cortisol requirements. The main precipitating factors are gastrointestinal diseases (GI infection, vomiting, and diarrhea) and other infectious disease.<br>• Patients with suspected adrenal crisis should be treated with an immediate parenteral injection of 100 mg hydrocortisone, followed by appropriate fluid resuscitation and 200 mg of hydrocortisone/24 hours (via continuous iv therapy or 6 hourly injection); If hydrocortisone is unavailable, prednisolone is suggested as an alternative. |
| **Additional monitoring requirements** [7,13, ‡] | • Outpatient visits in a specialised centre at the investigator's discretion<br>• Monitoring of any underlying hypothalamic-pituitary disease (not applicable to iatrogenic adrenal insufficiency) |
| **Education (as treatment often long term)** [5,14,15,16,17, ‡] | • Explain to patient and family the importance of:<br>  • Long-term replacement therapy<br>  • Need to increase usual glucocorticoid dose during stress and adrenal crisis-prevention strategies including parenteral self- or lay-administration of emergency glucocorticoids<br>  • Notifying medical staff if patients are to undergo any surgical procedure<br>• Consider to provide patients with a steroid emergency card and medical alert identification to inform health personnel of the need for increased glucocorticoid doses to avert or treat adrenal crisis and the need of immediate parenteral steroid |

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| | treatment in the event of an emergency.<br>• In addition, patients must always have supplies of hydrocortisone injections and should be taught how and when to administer them |

‡ This table was developed in consultation with practicing academic endocrinology physician experts. Furthermore, the following references apply:

**References:** 1. White and Arlt, 2010; 2. Chakera and Vaidya, 2010; 3. Faulhaber et al. 2011; 4. Oboni et al. 2013; 5. Quinkler et al. 2013; 6. de Miguel Novoa et al. 2014; 7. Arlt and Allolio, 2003; 8. Andrioli et al. 2006; 9. Asare 2007; 10. Shaikh et al. 2012; 11. Yip et al. 2013; 12. Zueger et al. 2014; 13. Banco et al. 2014; 14. Bornstein S et al., 2016; 15. Schweiger et al. 2010; 16. Baxter et al. 2013; 17. Charmandari et al. 2014.

## APPENDIX 12: SUGGESTED GLUCOCORTICOID CONVERSION TABLE

### Glucocorticoid Dose Conversion Table

| Glucocorticoid | Equivalent Dosage | Half-life |
|---|---|---|
| **Short-Acting** | | |
| Cortisone | 25 mg | 8 - 12 hours |
| Hydrocortisone | 20 mg | |
| **Intermediate-Acting** | | |
| Prednisolone | 5 mg | 18 - 36 hours |
| Prednisone | 5 mg | |
| Methylprednisolone | 4 mg | |
| Triamcinolone | 4 mg | |
| **Long-Acting** | | |
| Dexamethasone | 0.75 mg | 36 - 54 hours |
| Betamethasone | 0.6 mg | |

1. American Society of Health System Pharmacists (AHFS) Drug information 2014

2. Meikle AW and Tyler FH. Potency and duration of action of glucocorticoids. Am J of Med 1977;63;200.

Note: “Equivalent dosages” are general approximations, and may not apply to all routes of administrations (especially oral inhalation, intramuscular, or intrasynovial injections). In addition, duration of HPA-axis suppression must be considered.