Study Protocol *(amendment 2 of 23rd of January 2012)*

“A phase II, randomized, double-blind, placebo controlled study of Tocilizumab in patients with Giant Cell Arteritis”

**Sponsor**
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**Supporter**
Roche Pharma (Switzerland) Ltd

**Trial Design**
2-arm (Tocilizumab + Glucocorticoids (GCs) vs. Placebo + GCs), randomized, placebo-controlled, double blind

**Indication/Study population**
Giant Cell Arteritis (GCA)

**Target Population**
Patients with newly onset or relapsing Giant Cell Arteritis (GCA), satisfying ACR criteria AND an elevated sedimentation rate above 40 mm/h and a CRP > 20 mg/L and a biopsy proven GCA OR a large vessel vasculitis assessed by MR Angiography (MRA)

The study will be performed according to requirement of Good Clinical Practice (GCP)
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STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1. Giant Cell Arteritis (GCA)

Giant-cell arteritis (GCA) is an immune-mediated disease characterized by granulomatous infiltrates in the wall of medium-size and large arteries that mostly affects people older than 50 years of age. The annual incidence varies between 6 and 32 cases per 100,000 persons worldwide (1-5). Glucocorticoid (GC) treatment dramatically alters the symptoms and course of GCA, reducing the likelihood of vascular complications that could lead e.g. to blindness (6,7). However, relapses usually occur when GC dosages are tapered, resulting in frequent re-treatment with high cumulative dosages of GC over time with substantial toxicity and morbidity (e.g., diabetes mellitus, infections, enhanced cardiovascular risk, osteoporotic fractures, cataracts) (8-10). Moreover, standard corticosteroid regimens only partially suppress vascular inflammation. Smoldering disease activity may expose GCA patients to the risk of progressive vascular damage (e.g., formation of aortic aneurysms) (11). Therefore, novel therapies are needed that effectively reduce the dose and duration of GC treatment and provide more durable remissions of GCA. Other investigators have evaluated the utility of cytotoxic and anti-inflammatory agents in GCA. However, the reports have been anecdotal, or consist of uncontrolled studies, or of controlled studies with conflicting or negative results in terms of efficacy (12-14).

1.1.2. Tocilizumab

Tocilizumab (TCZ, RoActemra®) is a humanized IgG1κ monoclonal antibody directed against the human interleukin-6 receptor (IL-6R), comprising a murine complementarity determining region (CDR) and a human IgG1κ antibody framework. Tocilizumab binds specifically to both soluble and membrane-bound human IL-6R (sIL-6R and mIL-6R), and has been shown to inhibit both sIL-6R and mIL-6R mediated signalling. Interleukin-6 (IL-6) is a multifunctional cytokine, produced by a variety of cell types, including lymphocytes, monocytes and fibroblasts. It was originally identified as B cell stimulatory factor (BSF-2), which induces the final maturation of B cells into antibody producing cells. IL-6 is now known to be involved in a diverse number of physiological processes, including T cell activation, induction of acute phase proteins, stimulation of hematopoietic precursor cell growth and differentiation, proliferation of hepatic, dermal and neural cells, bone metabolism, lipid metabolism, and hepatoprotection.

Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders, including rheumatoid arthritis (RA), psoriasis, giant cell arteritis and Castleman’s disease. IL-6 is produced by synovial and endothelial cells, leading to local production in joints affected by inflammatory processes such as RA. In addition, IL-6 levels correlate with RA disease activity, and improvements associated with disease-modifying antirheumatic drug (DMARD) use are accompanied by a reduction in serum IL-6 levels. Inhibition of IL-6 and/or its receptor therefore represents a new and novel approach for the treatment of RA.

Clinical studies with tocilizumab have been performed or are ongoing in a number of disease areas, including adult onset RA, systemic-onset juvenile idiopathic arthritis (sJIA),
polyarticular-course juvenile idiopathic arthritis (pcJIA), SLE, Crohn’s disease, Castleman’s disease and multiple myeloma. The efficacy of tocilizumab in alleviating the signs and symptoms of RA have been assessed in five randomized, double-blind, multicenter studies, where tocilizumab was administered as monotherapy, in combination with MTX, or in combination with other DMARDs. These trials have demonstrated the efficacy of tocilizumab in RA patients with an inadequate response to anti-TNFs, MTX and other DMARDs, and in MTX-naive patients. Tocilizumab is approved in Japan for Castleman’s disease, adult RA (as monotherapy), pcJIA and sJIA. In Switzerland it is approved for adult RA.

1.2 Rationale

1.2.1. Rationale for the Study

Increased knowledge of cell types and mediators within the vessels damaged by GCA has led to speculation about the potential role of cytokine antagonists. Thus, excessive cytokine production (for example, of interleukin-1, TNFα and interleukin-6 from activated macrophages in the adventitial layer) induces systemic inflammation with an exuberant acute-phase response (15-18) that might be associated more with systemic inflammatory symptoms of the disease. In parallel, interferon-gamma, which is released by T cells captured in the arterial wall, activates tissue-injurious macrophages. In response to the immune injury, the artery generates hyperplasia of the intima that leads to luminal occlusion and subsequent tissue ischemia (19).

Published case studies reported that some patients with GCA or polymyalgia rheumatica who received the anti-TNFα agent infliximab had sustained remission and became GC-independent (20, 21). However, these promising observations were not confirmed by the results of a recently published randomized, placebo-controlled, double-blind, multicenter trial (22). A few pitfalls in the study design such as choice of maintenance strategy after GC-induced remission instead of remission induction in newly diagnosed active disease or too infrequent application of infliximab could have been responsible for failing to demonstrate superiority of anti-TNF treatment over placebo. Indeed, individual patients with GC-resistant GCA may come into longstanding remission upon anti-TNF treatment, if i.e. infliximab infusions are applied in regular 4 week intervals (unpublished own clinical observations).

Although there is information on multiple circulating cytokines, only IL-6 has shown consistent results within multiple studies (23-32). Polymyalgia rheumatica (PMR) and GCA are characterized by an aberrant production of IL-6, and GC therapy is followed by a significant decrease of IL-6 levels. From clinical experience it can be assumed that partial suppression of IL-6 is sufficient to control the systemic manifestations of these syndromes and to prevent most vascular complications in GCA. However, there are at least two observations that suggest that GC therapy does not affect the underlying disease mechanisms. First, although clinical symptoms are rapidly improved by GC therapy and acute phase proteins decrease, in many patients IL-6 levels do not return to normal values (11,26,27,33). And second, in patients with PMR in apparent complete clinical remission with GC, withdrawal of therapy results in relapse of disease within 48 h (25). In fact, in the TAB-SCID chimera model, doses equivalent to 30 mg/kg/day of prednisone in humans were required for complete suppression of IL-6 in the tissue (34). These findings are also consistent with anecdotal findings such as persistent arteritis in patients with long lasting and CC treated GCA (36) that might lead to increased risk of developing aortic aneurysms as additional longterm complication (35,36).
Similar to GCA, serum IL-6 levels have been reported to be greatly elevated in patients with Takayasu arteritis (TA) and to correlate positively with disease activity (37,38). This indicates that IL-6 may be a good target molecule in the treatment of TA. Assuming a pathogenetic role of IL-6, the humanized anti-IL-6 receptor (IL-6R) antibody, tocilizumab was used in one young female patient with refractory disease and led to improvement of clinical manifestations and abnormal laboratory findings after repetitive administration of 4 mg/kg every 1-2 weeks during 1 year and of 8mg/kg every 3 weeks thereafter over 5 years (39).

The principal aim of the present study will be to evaluate the efficacy and safety of tocilizumab + GC treatment compared to placebo + GC treatment in the induction and maintenance of disease remission in patients with newly diagnosed or relapsing GCA.

1.2.2. Rationale for the Study Design

This is a randomized, placebo-controlled, phase II study: an assessment of efficacy and safety of tocilizumab when given on a background of glucocorticoid (GC) medication. Although the safety profile of tocilizumab has been extensively studied, there is limited experience of this drug when used in GCA. This study proposes to administer tocilizumab in monthly intervals within 12 months.

The aim of the present study will be to evaluate the efficacy and safety of tocilizumab + GC treatment compared to placebo + GC treatment in the induction and maintenance of disease remission in patients with newly diagnosed or relapsing GCA. The clinically most relevant goals of treatment with tocilizumab in GCA will be 1) the rapid reduction of GC dosage (because of high GC-associated morbidity in the elderly population) without disease relapse within the first 3 months and 2) further tapering and discontinuation of GC from months 4 to 12. Complete remission of disease (normal ESR and CRP + absence of signs and symptoms) after 12 weeks at a GC dose of 0.1 mg/kg/d prednisone has been defined as primary outcome.

The benefit for patients on tocilizumab compared to placebo treatment is assumed to result from a higher probability of achieving remission within 3 months (induction period) combined with significantly less relapses and less cumulative dosage of GCs and less GC-associated toxicities/morbidities in the follow-up (maintenance period).

1.2.3. Rationale for Dosage Selection

We decided to accelerate standard GC dosage tapering during the induction period in this study, because 1) the high initial dosage and slow tapering of GCs as reflected by standard treatment is still associated with a substantial relapse rate (30% within 3 months) and with GC toxicity and morbidity in many patients (22), and because 2) of the rapid clinical and laboratory response reported in two patient with Takayasu arteritis (39) and in 5 patients with newly diagnosed or GC-resistant GCA (40) after initiation of tocilizumab treatment.

Patients in the verum group will receive a minimum of 24 weeks of therapy at the relevant tocilizumab dose, after which time the safety of tocilizumab treatment will be determined by the sponsor. Thereafter, patients will continue to receive tocilizumab up to 52 weeks provided that safety criteria had been fulfilled after 24 weeks. If warranted for safety reasons, the sponsor may also discontinue or reduce the dose of tocilizumab, at any time.

2. OBJECTIVES
2.1. **Primary Endpoint**

- Number of complete remissions of disease (normal ESR and CRP + absence of signs and symptoms) after 12 weeks at a GC dose of 0.1 mg/kg/d prednisone.

2.2. **Secondary Endpoints**

- Proportion of relapse free patients after 12 months
- Cumulative dose of GCs after 3, 6 and 12 months
- Time to stop of GCs
- Time to first relapse after induction of remission
- Cumulative CRP after 3, 6 and 12 months
- SF-12 after 3, 6 and 12 months

3. **COMMON PROCEDURES**

The screening visit can occur up to 10 days prior to receiving the first dose of study medication.

Patient eligibility will be determined at the baseline visit, and if all eligibility criteria are met, the patient will be randomized to a treatment group. The first dose of study medication should occur within 24 hours following the baseline assessments.

Study visits will occur at baseline, and at Weeks 2, 4, 6, 8, 10, 12, and every 4 weeks thereafter, with assessments performed as per the schedule of assessments.

Tocilizumab (8mg/kg)/placebo will be administered by intravenous (i.v.) infusion on Days 1, at weeks 4, 8, 12, thereafter every 4 weeks until week 52.

In addition, patients may continue to receive background oral GCs according to the tapering dosage regimen throughout the study as follows:

1. Week 1 mg/kg/d prednisone
2. Week 0.9 mg/kg/d
3. Week 0.8 mg/kg/d
4. Week 0.7 mg/kg/d
5. Week 0.6 mg/kg/d
6. Week 0.5 mg/kg/d
7. Week 0.4 mg/kg/d
8. Week 0.3 mg/kg/d
9. Week 0.25 mg/kg/d
10. Week 0.20 mg/kg/d
11. Week 0.15 mg/kg/d
12. Week 0.1 mg/kg/d

Followed by a maintenance dosage that is reduced by 1mg/d monthly down to zero during week 13 - 52.

All patients will receive the mandatory co-medication as follows:

- Low dose aspirin 100mg/d
- A proton pump inhibitor (PPI) in appropriate dosage within the first 8 weeks
- Calcium 1000 mg/d and cholecalciferol 800 U/d
- Ibandronate 3mg i.v. 3 monthly
3.1. Definition of Relapse

- Re-increase of ESR from normal (<20 mm) to 40 mm or greater in the first hour and of CRP from normal to 10 mg/L or greater, plus at least 1 symptom or sign of GCA:
- New or recurrent headache or pain or tenderness of the scalp or temporal artery
- New, recurrent or worsening of visual symptoms specific to GCA
- New or recurrent claudicatio of the tongue or jaw
- New, recurrent, or worsening of temporal artery signs and symptoms
- New, recurrent, or worsening transient cerebral ischemia
- New, recurrent, or worsening of classic polymyalgia rheumatica-like symptoms
- Sustained fever (temperature > 38°C for > 1 week)
- New, recurrent, or worsening of MR angiographic abnormalities
- Other symptoms specified by the individual assessor
- Other related symptoms specified by the investigator

3.2. Rescue Medication in Case of Relapse after Induction of Remission

Major relapse (visual worsening, claudicatio, TIA, headache or pain or tenderness of the scalp, temporal artery signs and symptoms): GC at the same dosing regimen as for induction therapy.

Minor relapse (fever, PMR-like symptoms, increase of ESR or CRP or platelets or angio-MRI abnormalities without clinical signs and symptoms of GCA reactivation): Resume treatment with the previous higher dose of prednisone that provided disease remission, plus 10mg/d. If the relapse resolves within 72 hours, the patient is to continue receiving that dosage for 2 weeks and then resume tapering according to the induction protocol.

3.3. Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. Patients should also be informed of the circumstances under which their participation may be terminated by the investigator without their consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure or any reason where it is felt by the investigator that it is in the best interest of the patient to be excluded from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

If the reason for removal of a patient from the study is an Adverse Event, the principal specific event will be recorded on the CRF. The patient should be followed until the Adverse Event has resolved, if possible.

If the patient is lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made with an explanation of why the patient is withdrawing from the study.

Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

If a patient withdraws from the study at any point he/she must complete a withdrawal visit, which should be conducted as specified in the Schedule of Assessments. If a patient withdraws at, or during, a scheduled or unscheduled visit, the visit should proceed as a withdrawal visit, and only the withdrawal visit assessments should be conducted. After the
withdrawal visit, the patient will be followed for at least 12 weeks after the last tocilizumab infusion.

Patients withdrawn from the study due to elevated liver function tests must have repeat tests performed in three to five days and then every two weeks until the levels are decreasing. Thereafter, patients must be followed on a monthly basis, until levels are within the normal range. If the patient’s liver function tests have not returned to normal within six months (or sooner, if deemed necessary by the investigator), the patient should be referred to a hepatologist as clinically indicated.

Patients withdrawn from the study due to an absolute neutrophil count (ANC) below 500 cells/µL must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, and must have a repeat WBC with differential performed weekly until the ANC is above 1500/µL. If the ANC does not return to above 1500/µL within 2 months (or sooner, if deemed necessary by the investigator), the patient should be referred to a hematologist as clinically indicated.

3.4. **End of Study**

The end of the study will be the date of the last patient last visit (LPLV).

3.5. **Number of Patients / Assignment to Treatment Groups**

A total of 27 patients, 18 randomly assigned to tocilizumab and 9 to placebo treatment.

3.6. **Centers**

This will be a monocentric study. Patients will be recruited from internal and external referrals to the in-and out-patient Department of Rheumatology, Clinical Immunology & Allergology, University Hospital, Inselspital, Bern, Switzerland.

3.7. **Duration of Treatment per Subject**

12 months

3.8. **Duration of Trial Recruitment**

24 months

3.9. **Randomization, Intervention and Drug/Placebo Preparation**

Patients are randomly assigned in a 2:1 ratio to receive tocilizumab or placebo. Patients receive infusions at weeks 0, 4, 8, 12 and every 4 weeks thereafter. Allocation to treatment group will be performed by using a central computerized randomization procedure. Allocation will be concealed using central randomization generated by CTU Bern according to the internal standard operating procedure (SPI_08, SCC_02). Responsible will be a senior statistician which is otherwise not involved in study conduct, monitoring or data analysis. Patients, investigators, and study personnel are blinded to treatment assignments during the study; the site oncology nurse, who prepares study medication, is not blinded to this information but has no direct patient contact.

The last recorded body weight of a patient should be used for calculating the volumes for each infusion. For the preparation of the infusion bag, 0.4 mL per kg of the patient’s body
weight will be withdrawn from a 100 mL bag of normal saline (0.9% w/v sodium chloride solution), using aseptic technique. This volume will be replaced in the saline bag with an equal volume of tocilizumab/placebo from the patient’s assigned study medication vials (as per above). To achieve the total calculated volume of tocilizumab required, at the appropriate dose, equal volumes must be withdrawn from each of the 4 or 8 vials. The infusion bag should be gently inverted to mix the solution without foaming. All study medication volumes must be recorded in the pharmacy records. Medication volumes and additional details of the infusion preparation are provided in the protocol supporting document.

The tocilizumab infusion preparation (‘ready for infusion’) will be immediately transferred from the Department of Medical Oncology to the Rheumatology Day Clinic. In case of delay the prepared infusion of study medication will be stored for 30 minutes at max and at 4°C before administration to study patients.

The tocilizumab infusion will be then administered at room temperature by controlled infusion into an arm vein over a 1 hour period. In exceptional cases this time may be extended to up to 6 hours.

The infusion speed must be 10 mL/hour for 15 minutes and then increased to 130 mL/h to complete the dosing over 1 hour. The entire 100 mL content of the infusion bag must be administered. Following the infusion of study medication, 20 mL of normal saline will be administered to flush the remaining study medication through the intravenous set.

Randomization will be done by the CTU Bern using a central computer generated procedure and will be stratified by the diagnosis (biopsy proven GCA or large vessel vasculitis).

The preparation/blinding of tocilizumab and placebo infusions will be done by a non-blinded nurse in the Department of Medical Oncology (Inselspital).

3.10. Planned interim safety analysis

6 months after First Patient First Visit (FPFV)

3.11. Condition to be fulfilled (approximate date)

12 months after FPFV (first patient first visit); investigated outcomes: rates of SAEs.

3.12. Estimated date of primary analysis

After last follow-up visit after 12 months

3.13. Planned long-term follow-up

none

4. Study Population

4.1. Overview

The target population for this study is adult patients > 50 years of age with biopsy proven giant cell arteritis (GCA) and/or large vessel vasculitis as assessed by angio-MRI. Inclusion and exclusion criteria will be strictly adhered to. Postmenopausal status of female patients (last menstrual period > 12 months ago)
4.2. **Inclusion Criteria**

Patients with newly onset or relapsing GCA and > 50 years of age, satisfying ACR criteria (12) AND an elevated sedimentation rate above 40 mm and a CRP > 20 mg/L

Patients with histologically proven GCA or with large vessel vasculitis assessed by MRI

Postmenopausal and not nursing status of female patients (last menstrual period > 12 months ago)

Patient’s written informed consent

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4.3. **Exclusion Criteria**

1. Rheumatic diseases (except for CPPD/chondrocalcinosis) other than GCA/Takayasu disease or polymyalgia rheumatica (i.e., RA, autoimmune connectivitides, other systemic vasculitides, a.o.)

2. Evidence of significant and/or uncontrolled concomitant disease such as, but not limited to, cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine (in particular diabetes mellitus) or gastrointestinal disorders (including previous complicated diverticulitis) which, in the investigator’s opinion, would preclude patient participation or impact the benefit-risk ratio

3. Diagnosis of GCA > 4 weeks before screening visit and beginning of GC treatment > 4 weeks before screening (not applicable for patients with relapsing disease), or when a patient received treatment with tocilizumab or with other biological agents (such as TNFα-blockers) within 3 months before screening.

4. Any condition or general state of health which, in the Investigator’s opinion, would preclude participation in the study

5. Actual or recent myocardial infarction (within the last 3 months before screening visit)

6. Significant cardiac disease (NYHA Class III and IV), known severe chronic obstructive pulmonary disease (COPD) (FEV1 < 50% predicted or Functional dyspnoe > Grade 3 on the MRC Dyspnoe Scale) or other significant pulmonary disease

7. Uncontrolled disease (such as asthma, psoriasis or inflammatory bowel disease) where flares are commonly treated with oral or injectable corticosteroids

8. Known active infection of any kind, or any major episode of infection requiring hospitalization or treatment with i.v. anti-infectives within 4 weeks of baseline or completion of oral anti-infectives within 2 weeks prior to baseline

9. History of deep space/tissue infection (e.g. fasciitis, abscess, osteomyelitis) within 52 weeks prior to baseline

10. Any surgical procedure, including bone/joint surgery within 8 weeks prior to baseline or planned within the duration of the study

11. History of serious recurrent or chronic infection (for screening for a chest infection a chest radiograph will be performed at screening if not performed within 12 weeks prior to screening)
12. Lack of peripheral venous access

13. Body weight > 150 kg or BMI > 35

14. Previous treatment with tocilizumab or any other biological agent

15. Treatment with any investigational agent within 28 days of screening or 5 half-lives of the investigational drug (whichever is the longer)

16. History of severe allergic or anaphylactic reaction to any biologic agent or known hypersensitivity to any component of tocilizumab (RoActemra)

17. Receipt of any vaccine within 28 days prior to baseline (a patient’s vaccination record and need for immunization prior to receiving tocilizumab/placebo must be carefully investigated)

18. Positive tests for hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HbcAb) or hepatitis C serology

19. Positive Quantiferon-TB® test for latent Tb without subsequent INH prophylaxis

20. Patients with active Tb which had to be treated for Tb within 2 years before the screening visit

21. Absolute neutrophil count (ANC) < 2.0 x 10³/µl, white blood cells < 2.5 x 10⁹/µl, platelet count < 100,000/µl

22. Hemoglobin < 8.0 g/dl

23. Concentrations of serum IgG and/or IgM below 5.0 mg/mL and 0.40 mg/mL, Respectively

24. Serum creatinine > 2.0 mg/dL (200 µmol/L)

25. Alanine aminotransferase (ALT) or aspartate amino-transferase (AST) > 1.5 times the upper limit of normal (ULN)

26. Total bilirubin > 1.5 times the upper limit of normal (ULN)

27. Triglycerides > 400 mmol/dL (non-fasted) or > 250 mmol/dL (fasted) at screening

28. Premenopausal status and nursing

29. Claustrophobia (for MR-angiogram)

30. Known allergy against the contrast media (Multihance® or Dotarem® as alternative)

4.4. Assessments at screening and before each infusion

1. Vital signs (pulse rate, respiration rate, blood pressure)

2. Questionnaire regarding B-symptoms (fever, weight loss > 2kg, nightly sweating)
3. Questionnaire regarding signs and symptoms (headache, tenderness of the scalp, claudication of tongue, jaw, upper and lower limbs, visual impairment/loss)

4. General physical exam

5. Clinical exam of large vessels (palpation of Aa.temporales, bilateral auscultation of Aa.carotides, subclavia, axillares, brachiales, femorales and of Aorta abdominalis) and tenderness of the scalp/A.temporalis

6. Bilateral measurement of blood pressure

7. SF-12

8. ESR, CRP, plasma + serum (each 5ml), total blood cell counts, HbA1c (only every 3 months), blood glucose and blood lipids (fasted, only after 3, 6 and 12 months), alkaline phosphatase, ASAT, ALAT, creatinine, urine sediment and status, plasma sample (every visit), Quantiferon testing for latent Tb and screening for hepatitis B and C (before screening visit)

4.5. Further Assessments

1. Duplex ultrasound of Aa.temporales or other vessels that are clinically affected before the screening visit and after 3 months and at any time of relapse

2. Biopsy of the temporal artery (before the screening visit) in local anesthesia

3. In case of negative biopsy of the temporal artery, MR angiography of thoracic and/or abdominal aorta and its branches will be performed before the screening visit, after 3 and 12 months and at any time of clinical relapse in patients with ‘occult aortitis/GCA’
### 4.6. List of study procedures

| Visit          | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 | Visit 12 | Visit 13 | Visit 14 | Visit 15 | Visit 16 | Visit 17 | Visit 18 |
|---------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|----------|----------|----------|
| **Timing**    | Day 0   | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     | Date     |
| **TCZ/placebo**| Administration** and sampling (AS) | Screening | AS1 | AS2 | AS3 | AS4 | AS5 | AS6 | AS7 | AS8 | AS9 | AS10 | AS11 | AS12 | AS13 | Follow-up and Study Conclusion |
| Informed Consent** | ● | | | | | | | | | | | | | | | | | | |
| Check eligibility Criteria** | ● | | | | | | | | | | | | | | | | | | |
| Medical History* | ● | | | | | | | | | | | | | | | | | | |
| Complete physical examination* | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Disease oriented physical examination* | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Randomization** | ● | | | | | | | | | | | | | | | | | | |
| Check elimination criteria** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Check contraindications** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Vital signs** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| ESR, CRP (10ml)* | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Plasma sample (5ml)** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| EDTA whole blood (5ml)** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Hematology (5ml)* | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Biochemistry (10ml)* | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| Lipids (5ml)** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |
| IgG, IgM (5ml)** | ● | | | | | | | | | | | | | | | | | | |
| Urine microscopic * exam + Dipstick | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | | |

** TCZ/placebo Administration** and sampling (AS)

* AS1 to AS13 correspond to the study procedures at each visit.

** Follow-up and Study Conclusion
**SF-12**

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<th>Procedure / Medication</th>
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<td>Duplex sonography if + before screening**</td>
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<td>Recording of AEs by Investigator**</td>
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<td>Reporting of SAEs**</td>
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* is used to indicate a study procedure that requires documentation in the individual CRF.

The total blood volume that is drawn for laboratory investigations during the study is 700 ml (300 ml within the first 3 months).

All examinations are study specific except for distinct lab exams (ESR, CRP, hematology, biochemistry) at baseline, after 2, 4, 6, 9 and 12 months that would be also routinely performed (standard care).

* These laboratory exams will be performed as routine standard of care at baseline, after 3, 6, 9 and 12 months and are therefore reimbursed; at all additional time points these exams are study specific and costs are covered by the study budget.

** These exams are study-specific and costs are covered by the study budget.

- all laboratory investigations and histological analyses are performed *in-house* at the University Hospital of Bern/Inselspital

- MRAa of the thoracic and abdominal aorta after 3 and 12 months are performed with using contrast media (Multihance® or Dotarem®) at the Department of Diagnostic Radiology of the University Hospital of Bern, Inselspital.

**Randomization procedure and labels of study medication**

Allocation will be concealed using central randomization generated by CTU Bern according to the internal standard operating procedure (SPI_08, SCC_02). Responsible will be a senior statistician which is otherwise not involved in study conduct, monitoring or data analysis.

**Label of study medication:** enclosed as APPENDIX
4.7. Data and safety monitoring

Data monitoring is performed by the Clinical Investigation Unit (CIU) of the University of Bern. Safety monitoring during the entire study will be monthly done by an independent Safety Monitoring Board that consists of an experienced clinician in internal medicine (Dr. Martin Perrig, Deputy Director of the University Clinic of General Internal Medicine at the University Hospital, Inselspital Bern) and an clinical epidemiologist and statistics expert (Dr. Sven Trelle, Co-Director of the Clinical Trial Unit of the University of Bern). Thus, safety analyses don’t jeopardize the blinding.

5. Drug related side effects

5.1. Tocilizumab

Patients should be informed of the risks associated with taking tocilizumab. Below are listed specific major risks that patients need to be aware of.

Infections

Tocilizumab treatment should not be initiated in patients with active infections. Caution should also be exercised when considering the use of tocilizumab in patients with a history of recurring infection or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended, as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. Patients should be instructed to contact a physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Administration of tocilizumab should be interrupted if a patient develops a serious infection until the infection is resolved.

Complications of Diverticulitis

Rare events of diverticular perforations as complications of diverticulitis have been reported. Tocilizumab should be used with caution in patients with a previous history of intestinal ulceration or diverticulitis, and patients with previous complicated diverticulitis are excluded from this trial. Patients presenting with symptoms of abdominal pain should be evaluated promptly for early identification of gastrointestinal perforation.

Tuberculosis (TB)

Patients with active TB requiring treatment within 2 years prior to the screening visit are excluded from this trial.

As recommended for other biologic therapies, patients should be screened for latent tuberculosis infection prior to starting tocilizumab therapy. Patients with a positive TB test result (using the QuantiFERON-TB® test) at screening are excluded (unless treated with anti-TB therapy for at least 4 weeks prior to receiving study medication and a chest radiograph is negative for active TB). Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating tocilizumab.
Immunization
Live and attenuated vaccines should not be given concurrently with tocilizumab as clinical safety has not been established.

No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab.

Hypersensitivity Reactions
Serious hypersensitivity reactions have been reported in association with infusion of tocilizumab in 0.3% of patients. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration of tocilizumab. Patients with a history of severe allergic or anaphylactic reaction to any biologic agent, or known hypersensitivity to any component of tocilizumab, are excluded from this study.

Active Hepatic Disease and Hepatic Impairment
Treatment with tocilizumab may be associated with elevations in hepatic transaminases. Patients with ALT or AST > 1.5 times the upper limit of normal (ULN) at screening are therefore excluded from this study. Patients should be monitored for signs of hepatic impairment throughout the study. If a patient experiences elevated liver transaminases, the dose of tocilizumab should be reduced or discontinued.

Hyperlipidemia
Increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been observed. Patients with triglycerides > 400 mg/dL (non-fasted) or > 250 mg/dL (fasted) at screening are therefore excluded from this study. Lipid parameters should be monitored throughout the study following initiation of tocilizumab therapy. Patients should be managed according to local clinical guidelines for the management of hyperlipidemia.

Drug Interactions
The formation of CYP450 enzymes is suppressed by the cytokines stimulating chronic inflammation such as IL-6. Thus it is expected that with administration of tocilizumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, or where the dose is individually adjusted. Upon initiation and discontinuation of tocilizumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine) should be performed and the individual dose of the medicinal product adjusted as needed.

Co-administration of tocilizumab with simvastatin has been shown to reduce the plasma concentration of simvastatin in RA patients. Cholesterol levels should be periodically monitored and dosage adjustments of simvastatin may be required (please refer to the Summary of Product Characteristics for simvastatin).

Dose modification procedures in case of tocilizumab toxicity
The dose of tocilizumab must be modified for the following toxicities:

Dose Modification for Liver Toxicity
Elevated ALT or AST:
- For persistent increases of > 1 – 3 × ULN in spite of dose modification of tocilizumab should be considered in order to normalize ALT/AST levels.
- Patients who experience an increase in ALT or AST ≥ 3 times the upper limit of normal (ULN) should stop treatment with tocilizumab. Blood samples should be taken every two weeks thereafter. Once the patient’s ALT and AST are below 3 × ULN, study treatment should recommence at the next scheduled 2 - 4 weekly visit.
- If the patient has a second ALT or AST elevation ≥ 3 times the ULN on recommencing treatment, treatment with tocilizumab must be permanently discontinued.
- If a patient has an ALT or AST elevation more than 2 × ULN but less than 3 × ULN, a blood sample should be taken just prior to the next dose of tocilizumab to verify that the ALT and AST remain below 3 × ULN.
- In the event that a patient’s ALT or AST is elevated to more than 5 × ULN, treatment with tocilizumab must be permanently discontinued.
- If two consecutive doses of tocilizumab are missed due to ALT or AST elevations, treatment with tocilizumab must be permanently discontinued.

Dose Modification for Infections
- Clinical signs which should warn the investigator of possible drug toxicity include severe infection or frequent minor infections, mucositis and pneumonitis. The investigator must report such signs to the sponsor and provide appropriate treatment. If a patient develops a serious infection, treatment with tocilizumab must be interrupted until the infection is considered completely resolved.

Dose Modification for Neutropenia
- If a patient’s absolute neutrophil count (ANC) decreases to < 0.5 × 10⁹/L (500/µL), treatment with tocilizumab must be permanently discontinued.
- If the ANC decreases to < 1 × 10⁹/L but is > 0.5 × 10⁹/L, treatment should be interrupted. Once the neutrophil count is > 1 × 10⁹/L, treatment may recommence.

Dose Modification for Thrombocytopenia
- Platelets should be monitored during treatment with tocilizumab. If the platelet count is less than 100,000/µL but > 50,000/µL, tocilizumab must be interrupted. Once the platelet count is > 100,000/µL, treatment with tocilizumab can recommence.
- Tocilizumab must be discontinued if the platelet count decreases to below 50,000/µL.

Dose Modification For Infusion Related Reactions
If a patient experiences any sign(s) or symptom(s) of an infusion reaction during the infusion and the patient remains hemodynamically stable:
- The infusion rate must be slowed down (at least halved) and the infusion time extended.
- If the patient continues to display any sign(s) or symptom(s) of hypersensitivity, an intramuscular or slow intravenous dose of an antihistamine must be administered.
- In patients who experience life-threatening infusion reactions with cardiovascular collapse, the infusion must be discontinued, and the patient must be treated as for an anaphylactic reaction, with intravenous antihistamines, corticosteroids and adrenaline, if necessary. No further tocilizumab must be given, and the patient must be withdrawn from the study.
If the tocilizumab dose is held due to any of the toxicities described above, all other study assessments should be performed for the study visit, as per the schedule of assessments.

**Pregnancy**

There are no adequate data from the use of tocilizumab in pregnant women. When tocilizumab was administered intravenously to cynomolgus monkeys during early gestation, no direct or indirect harmful teratogenic effects on pregnancy or embryo-fetal development were observed. However, in an embryo-fetal toxicity study conducted in cynomolgus monkeys, a slight increase in abortion/embryo-fetal death was seen with high systemic exposure (> 100 times human exposure) compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for either fetal growth or the immunological control of the maternal/fetal interface, a relation of this finding to tocilizumab cannot be excluded. The potential risk for humans is unknown.

It is not known whether tocilizumab is excreted in human breast milk. However, given that maternal IgG enters breast milk, tocilizumab should not be administered to nursing mothers.

Basically, the target female population of this study will only include postmenopausal individuals.

Male patients: For contraception of premenopausal female partners of male patients that participate in the study those have to use a condom during sexual intercourse.

### 5.2 Glucocorticoids (GCs)

Patients should also be informed of the risks associated with taking glucocorticoids. Below are listed specific major risks that patients need to be aware of:

- Glucocorticoids can cause immunosuppression with enhanced risk for bacterial and viral infections, hypertension, diabetes mellitus, cataracts, glaucoma, bruising, thinning of the skin, weight gain, psychological changes, osteoporosis, accelerated atherosclerosis, increased risk of gastrointestinal bleeding, aseptic necrosis of bone and adrenal insufficiency. Although rare, steroid-induced hypersensitivity reactions do occur. They range from minor rashes to the more serious cardiovascular collapse. For additional safety data, refer to the local label.

- Well-controlled reproductive studies with glucocorticoids have not been performed in humans, but high doses of glucocorticoids given during pregnancy have caused hypoadrenalism in newborns.

### 6. Handling of Safety Parameters

#### 6.1. Definition and Reporting of Serious Adverse Events (Immediately Reportable)

Any clinical adverse event or abnormal laboratory test value that is **serious** and which occurs during the course of the study, irrespective of the treatment received by the patient, or the causality to study medication(s), must be reported to KEK, Swissmedic and Roche within **one** working day of the investigator becoming aware of the event (expedited reporting). For reporting purposes, the investigator must complete the **SAE Reporting Form** and forward it to the SAE Responsible.

In addition, related SAEs **MUST** be collected and reported, regardless of the time elapsed from the last study drug administration, even if the study has been closed.
This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

A Serious Adverse Event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- is fatal; [results in death**; NOTE: death is an outcome, not an event];
- is Life-Threatening [NOTE: the term “Life-Threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe];
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

** The term sudden death should only be used when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.

Any clinical adverse event or abnormal laboratory test value that is serious occurring during the course of the study, or during safety follow-up (SFU) of 12 weeks after the last administration of study medication, irrespective of the treatment received by the patient, or the causality to study medication, must be reported to Roche, KEK and Swissmedic within one working day of knowledge (expedited reporting)

For all serious infectious adverse events reported, the following should be determined within 48 hours of the adverse event becoming serious: WBC and differential, platelets, and should be recorded on the CRF, along with all signs and symptoms of the infection. Whenever possible, the relevant pathogen(s) should be identified and recorded on the CRF.

The study will comply with all local regulatory requirements and will adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting with the following exceptions:

For the purpose of this study, the following will not be considered SAEs:

- Elective hospitalizations or surgical procedures that are a result of a patient’s pre-existing condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones, joint replacement surgery, and diagnostic testing. Such events should still be recorded as medical procedures in the CRF.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening, or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These are usually considered as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions without hospitalization, treatment of an active infection with i.v. antibiotics without hospitalization, malignancies which are excised and considered cured without hospitalization, and development of drug dependency or drug abuse.
Please note, the term severe is a measure of intensity; thus a severe adverse event is not necessarily serious. For example, nausea of several hours duration may be rated as severe, but may not be clinically serious.

6.2. Definition of Adverse Events (AEs)

ICH E6 GCP guidelines define an AE as any untoward medical occurrence in a subject or subject administered a pharmaceutical product in a clinical investigation regardless of its causal relationship to the study treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of the investigator and other study personnel during study visits and interviews or by a study recipient presenting for medical care. All AE must be graded for intensity and relationship to study product and will be assessed by the Investigator using the following definitions:

- **Mild**: events require minimal or no treatment and do not interfere with the subject’s daily activities
- **Moderate**: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe**: events interrupt a subject’s usual daily activity and may require systemic drug therapy or other treatment. Severe vents are usually incapacitating.
- **Life threatening**: the subject’s life is at risk from the event.

Changes in the severity of AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator will decide if AEs are related to the administered products. The assessment of causality will be made using the following definitions:

- **Unrelated**: This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possible or Probable.
- **Unlikely**: In general, this category is applicable to an AE which meets the following criteria (must have the first two):
  1. It does not follow a reasonable temporal sequence from administration of the drug.
  2. It may readily have been produced by the subject’s clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
  3. It does not follow a known pattern of response to the suspected drug.
  4. It does not reappear or worsen when the drug is re-administered.
- **Possible**: This category applies to AEs in which the connection with the investigational product administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possible if, or when (must have the first two):
  1. It follows a reasonable temporal sequence from administration of the drug.
  2. It may have been produced by the subject’s clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
  3. It follows a known pattern of response to the suspected drug.
- **Probable**: This category applies to AEs which are considered to be related to the investigational product with high degree of certainty. An AE may be considered probable, if (must have the first three):
  1. It follows a reasonable temporal sequence from administration of the drug.
  2. It cannot be reasonably explained by the known characteristics of the subject’s clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
  3. It disappears or decreases on cessation or reduction in dose.
  4. It follows a known pattern of response to the drug.
5. It reappears on re-challenge.
6. All AEs will be followed up until adequate resolution.

6.3. **Definition of Suspected Unexpected Severe Adverse Event (SUSAR)**

SUSAR is an unexpected adverse reaction that
(a) results in death
(b) is life-threatening
(c) requires hospitalization or prolongation of existing hospitalization
(d) results in persistent or significant disability or incapacity
(e) consists of a congenital anomaly or birth defect

Any SUSAR occurring during the course of the study, or during safety follow-up (SFU) of 12 weeks after the last administration of study medication, irrespective of the treatment received by the patient, or the causality to study medication, will be reported to Roche, KEK and Swissmedic within one working day of knowledge (expedited reporting).

6.4. **Pregnancy**
Pregnant or breast feeding females are excluded from enrolling into this study.

7. **Statistical Considerations and Analytical Plan**

7.1. **Study Endpoints**

The primary treatment period is 12 weeks, and the main statistical analyses will be performed by the Clinical Trial Unit (CTU). The thorough analysis will be performed using all study data at the end of the study (LPLV). The sponsor will remain blinded to the results at the 12 week analysis.

The first database lock will occur for the purposes of the Week 12 primary efficacy analysis, when all patients have either completed at least 12 weeks of treatment or have withdrawn into safety follow up. Treatment assignments will be unblinded to the sponsor after completion of the interim analysis. A second database lock will occur once all patients have completed 52 weeks of treatment.

The sections below describe the primary and secondary endpoints for the Week 12 analyses and the Week 52 analyses.

The primary and secondary endpoints will be as follows:

**7.1.1. Primary Endpoint**
See 2.2

**7.1.2. Secondary Endpoints**
See 2.3

**7.2. Statistical and Analytical Methods**

**7.2.1. Statistical Model**

**7.2.1.1. Sample Size**
The study was designed with a planned sample size of 27 patients (9 in the placebo and 18 in the tocilizumab group). The power calculations were based on a chi-square test with no stratification and a type I error rate of 5%. The power of the study was expected to be greater...
than 80% if the relapse-free response rate = complete remission rate was approximately 90% in the tocilizumab group and approximately 30% in the placebo group (12,13,22,41,42).

7.2.2. Analysis Populations

Analysis will occur once all patients have reached week 12, and will be repeated once all patients have reached week 52. One patient population will be defined for the purpose of the safety analysis, and one for the efficacy analysis, at both time points.

7.2.2.1. Safety Population

The safety population will include all patients who are randomized and have received any part of an infusion of study medication. Patients who receive the incorrect therapy from that intended will be summarized in the group according to the therapy actually received.

This population will be used for all summaries of safety data (adverse events, serious adverse events, laboratory data).

7.2.2.2. Intent to Treat (ITT) Population

All patients randomized who have received any part of an infusion of study medication will be included in the ITT analysis.

The ITT analysis will be performed for all efficacy parameters.

Patients who prematurely withdraw from the study for any reason and for whom an assessment is not performed, for whatever reason, will still be included in the ITT analysis. Patients who receive an incorrect therapy from that intended will be analyzed in the group according to the intended randomized treatment group.

7.2.3. Efficacy Analysis

7.2.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of patients that have achieved complete remission of disease (normal ESR and CRP + absence of signs and symptoms) at Week 12 at a GC dose of 0.1 mg/kg/d of prednisone.

We will report treatment effects as difference in proportions (crude risk difference) and corresponding 95%-Confidence Intervals (CIs). P-values will be derived by Fisher’s exact test. The LOCF imputation method will be used to calculate ESR and CRP.

In a sensitivity analysis, we will use three additional scenarios: a) per protocol analysis; b) best case scenario (all treatment success in the tocilizumab group and all non-responders in the placebo group); c) worst case scenario (all non-responders in the tocilizumab group and all treatment success in the placebo group).

We will plot cumulative flare-free survival curves, according to the Kaplan-Meier method, and comparing them with a Cox-model.

7.2.3.2. Secondary Endpoints and Analyses

The following secondary endpoints will be presented:
1. The proportion of patients that remained relapse-free after 52 weeks will be compared between treatment groups using the same analysis described for the primary endpoint. We will report treatment effects as difference in proportions (crude risk difference) and
corresponding 95%-CIs. The imputation method will be as described for the primary endpoint.

2. The cumulative dose of GCs after 24 and 52 weeks will be summarized over time by treatment group using descriptive statistics and the difference in cumulative GC dose with corresponding 95-CIs will be reported. The imputation method will be as described for the primary endpoint.

3. The median time to the first relapse will be summarized over time by treatment group using descriptive statistics and the difference in the median time with corresponding 95-CIs will be reported. The imputation method will be as described for the primary endpoint.

4. Cumulative CRP levels after 24 and 52 weeks will be summarized over time by treatment group using descriptive statistics and the difference in CRP with corresponding 95-CIs will be reported. The imputation method will be as described for the primary endpoint.

5. The SF-12 after 12, 24 and 52 weeks will be summarized over time by treatment group using descriptive statistics and the difference in SF-12 with corresponding 95-CIs will be reported. The imputation method will be as described for the primary endpoint.

7.2.4. Safety Data Analyses

Adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and their corresponding preferred terms and body systems assigned. Adverse events will be summarized by treatment group and by body system. Details of withdrawals, including the reasons for withdrawal, will be summarized by treatment group. Deaths will be summarized by treatment group. Vital sign data will be summarized over time by treatment group. Changes from baseline at each visit for each vital sign parameter will be summarized using descriptive statistics. Laboratory data will be summarized over time by treatment group. Changes from baseline at each visit for each laboratory parameter will be summarized using descriptive statistics. All safety data will be listed by treatment group.

Safety analyses will be monthly performed by the Safety Monitoring Board as mentioned above.

8. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The sponsor is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, integrity and validity of the data recorded on the case report forms. The monitoring team of the Clinical Investigation Unit (CIU) will help the investigator and the sponsor to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial. At regular intervals during the trial, a representative of the monitoring team will review study progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. During these monitoring visits, the following but not exhaustive list of points will be scrutinized: patient informed consent, patient recruitment and follow-up, serious adverse event documentation and reporting, investigational product allocation, patient compliance with the investigational product regimen, investigational product accountability, concomitant therapy use and check of the case report form entries against the source
documents, except for the source data directly recorded in the case report form quality of data.

An independent person within the Clinical Trial Unit/CTU that is not involved in the practical conduct of the study will be responsible of blinding and randomization.

9. Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. An accurate running inventory of study drug will be kept by the site, and will include the CSI number(s), the numbers of prefilled flasks dispensed by Roche, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Department of Medical Oncology of the University Hospital of Bern throughout the study and at the site closeout visit. All used and unused supplies must be inventoried and accounted by a representative of Roche. A copy of the Drug Accountability Form will be also be included in the shipment. The investigator agrees not to supply study drug to any person not enrolled in the study or not named as a sub-investigator.

10. Subject Data Protection

Subjects will be informed that their clinical data is held on file at the site, that this source of information may be viewed by the staff of the CRO (including, where necessary, staff of the CRO other than the named Investigators), and that data may not be sighted by the Grant Provider Roche. Subjects will be similarly be informed that information from the study will be prepared and may also be submitted to government agencies and perhaps for publication. However, participants of the study will be only identified in such reports by their study identification number and perhaps their gender and age. The PI undertakes to hold all personal information in confidence.

11. Data Access

Subjects data files (CRFs) are stored in a closed cupboard at the site and can directly accessed by the PI, named sub-investigators, delegates of the CRO other than the PI, and by representatives of the KEK and of Swissmedic on demand at any time.

12. Data Archiving

Subjects data files (CRFs) and all other study documents are stored and archived for at least ten years at the study site.

13. References


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