CLINICAL STUDY PROTOCOL

A Randomized Multi-Center, Double-Blind, Placebo-Controlled Study of a New Modified-Release Tablet Formulation of Prednisone (Lodotra®) in Patients with Rheumatoid Arthritis

Circadian Administration of Prednisone in RA

The CAPRA-2 Study

Development Phase: Phase III
Protocol No.: NP01-007

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PROTOCOL SYNOPSIS

Study title:
A randomized multi-center, double-blind, placebo-controlled study of a new modified-release (MR) tablet formulation of prednisone (Lodotra®) in patients with rheumatoid arthritis (RA).

Indication:
Rheumatoid Arthritis (RA)

Protocol Number:
NP01-007

Investigator(s):
Coordinating Investigator: Prof. Buttgereit, Berlin, Germany

Study Sites:
Approximately 40 to 45 in North America and Europe

Clinical Phase:
III

Study Period:
Planned duration of the study (for each patient): 13 weeks
Planned recruitment period: 6-9 months
The actual overall study duration or patient recruitment period may vary.

Objectives:
- To evaluate if 12 weeks of treatment with 5 mg MR prednisone (Lodotra®) administered in the evening is superior to placebo in terms of the American College of Rheumatology (ACR)20 responder rate
- To evaluate if 12 weeks of treatment with 5 mg MR prednisone (Lodotra®) administered in the evening is superior to placebo in terms of the relative reduction of morning stiffness
- To investigate the safety and tolerability of the MR prednisone formulation (Lodotra®)

Methodology:
Randomized, multicenter, double blind, placebo-controlled, parallel-group study. After a single-blind 1 week screening phase, patients will be randomized to one of the two study treatments for 12 weeks of treatment (see flow chart on page 11).

Number of patients:
Approximately 350 patients will be enrolled in order to randomize 294 patients.
Diagnosis and criteria for inclusion:

Diagnosis:
- Rheumatoid Arthritis (RA)

Inclusion criteria:
To be eligible for the study, patients must meet the following criteria:
- Provide written informed consent
- Have a documented history of RA (sero-negative or sero-positive) in agreement with the ACR criteria including the symptoms morning stiffness, joint pain, tender and swollen joints, inflammatory state with elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
- Be on disease modifying anti-rheumatic drugs (DMARD) treatment for RA for at least 6 months, with a stable dose for at least 6 weeks prior to screening visit (Visit 0)
- Have duration of morning stiffness of at least 45 minutes
- Have swollen joint count of 4 or more out of 28
- Have tender joint count of 4 or more out of 28
- Aged 18 to 80 years
- Female patients of childbearing potential must be using a medically accepted contraceptive regimen
- Able to perform the required study procedures including handling of medication containers and diaries

Exclusion criteria:
The presence of any of the following will exclude a patient from study enrolment:
- Suffering from another disease, which requires glucocorticoid treatment, e.g. asthma or neurodermatitis
- Synovectomy within 4 months prior to study start
- Use of glucocorticoids (by any route) within 6 weeks prior to screening visit (Visit 0)
- Use of biologicals: tumor necrosis factor α (TNFα) inhibitors within 3 months prior to screening visit (Visit 0) or other compounds within 1 year prior to screening Visit 0
- Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation
- Pregnancy or nursing
- Participation in another clinical study (use of an investigational product) within 30 days preceding Visit 0
- Re-entry of patients previously enrolled in this trial
- Suspected inability or unwillingness to comply with study procedures
- Alcohol or drug abuse
- Requirement of nonpermitted concomitant medication
- Known hypersensitivity to prednisolone
- Any contraindication for low dose prednisone treatment
- Significant renal impairment (serum creatinine > 150 μmol/L)
- Significant hepatic impairment (investigator’s opinion)
Any uncontrolled concomitant disease requiring further clinical evaluation (e.g. uncontrolled diabetes, uncontrolled hypertension etc.)

**Randomization criteria:**
Patients must meet all of the following randomization criteria to be eligible for randomization into the double-blind treatment period at the randomization visit:

- Symptomatic status required for randomization:
  - Duration of morning stiffness of 45 minutes or more (on at least 4 days within the last 7 days)
  - Swollen joint count of 4 or more out of 28
  - Tender joint count of 4 or more out of 28
- Adequate compliance in completing study diaries
- Medication compliance (± 1 tablet of the calculated tablet range)
- Negative Hemoccult/guaiac test

**Duration of treatment:**
- Screening period: 1 week
- Treatment period: 12 weeks

**Test product, dose and mode of administration:**
- 5 mg MR tablet formulation of prednisone (Lodotra®)

**Reference product (placebo):**
- Matching placebo to 5 mg MR prednisone (Lodotra®)

**Dosing:**
At 10 p.m. (± 30 minutes): 1 x 5 mg MR prednisone tablet (or matching placebo)

**Concomitant Medication:**
**Not allowed:**
- Glucocorticoids other than the study medication
- Intra-articular injections and synoviorthesis
- Biologicals
- Initiation of DMARD therapy
- Initiation of non-steroidal anti-inflammatory drug (NSAID) therapy

**Allowed:**
- DMARDs on a stable dose (if already taken for at least 6 months prior to study start)
- NSAIDs on a stable dose (if already taken prior to study start)
- Other drugs for the treatment of concomitant diseases are allowed, however their dosage should be kept constant throughout the study
- Paracetamol/acetaminophen and other non-anti-inflammatory painkillers
Criteria for evaluation:
Efficacy:
Primary variable:
- ACR20 responder rate

Key secondary variable:
- Reduction of morning stiffness duration

Secondary variables:
- Disease Activity Score (DAS28 score)
- European League Against Rheumatism (EULAR) response criteria
- Individual core set measures
  - Tender joint count
  - Swollen joint count
  - Patient’s assessment of pain
  - Patient’s global assessment of disease activity
  - Physician’s global assessment of disease activity
  - Functional Disability Index of the Health Assessment Questionnaire (HAQ-DI)
  - ESR and CRP
- Severity of morning stiffness (visual analogue scale [VAS])
- Recurrence of stiffness during day
- Requirements for additional analgesics
- Pain (VAS, morning and evening)
- Fatigue (Functional Assessment of Chronic Illness Therapy [FACIT])
- Quality of life (Short Form [SF]-36)
- Inflammatory cytokines (interleukin-6 [IL-6] plus TNFα)

Safety:
- Adverse events (AEs)
- Changes in physical examination findings
- Changes in vital signs (blood pressure, pulse rate, body weight)
- Changes in laboratory values

Statistical Methods:

The primary efficacy analysis (ACR20 response rate) will be performed using logistic regression with treatment and (pooled) sites as factors. Patients who withdraw from the study prematurely will be considered non-responders with respect to the primary endpoint.

The relative change in morning stiffness and the absolute changes in the ACR core set measures will be analyzed using analysis of covariance (ANCOVA) with treatment and (pooled) sites as factors and the relevant baseline score as a covariate.
The time to a patient’s first response according to the ACR20 criteria will be analyzed using Kaplan-Meier methodology and the treatments will be compared using the log-rank test.

EULAR response rate and the proportion of patients taking additional analgesics will be analyzed using logistic regression with treatment and (pooled) sites as factors.

Safety data will be summarized by absolute and relative frequencies. In addition, shift tables will be provided for urinalysis results.

**STUDY FLOW CHART**

Visit 0  Visit 1  Visit 2  Visit 3  Visit 4
Week -1  Week 0  Week 2  Week 6  Week 12

---

1-Week Screening Phase  

5 mg Lodotra®

Placebo

DMARDs at a Stable Dose

Concomitant Medications at a Stable Dose

12-Week Treatment Phase
## STUDY SCHEDULE

<table>
<thead>
<tr>
<th>Visit</th>
<th>Visit 0</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
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<tbody>
<tr>
<td>Week</td>
<td>-1</td>
<td>0</td>
<td>2</td>
<td>6</td>
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<td>Medical history</td>
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<td>Previous medication</td>
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<tr>
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<td>Inflammatory cytokines (IL6 and TNFα)</td>
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<td>Dispense Hemoccult/guaiac Test</td>
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<td>Collect and develop Hemoccult/guaiac Test</td>
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<tr>
<td>Dispense study medication</td>
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<tr>
<td>Fix appointment for next visit</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dispense, collect and review study diaries</td>
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<td>✓</td>
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<tr>
<td>Adverse events</td>
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<td>Assess compliance</td>
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<tr>
<td>QoL questionnaire (SF-36)</td>
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<td>Randomization criteria</td>
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<tr>
<td>Randomization and fax confirmation</td>
<td>✓</td>
<td></td>
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<tr>
<td>Collect unused medication</td>
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<td>✓</td>
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<tr>
<td>Switch to immediate release prednisolone</td>
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</tbody>
</table>
a: All medication taken within the last 30 days before Visit 0 should be documented. In addition, previous medication for treatment of RA taken within the last 6 months before Visit 0 is documented.

b: Determine following factors contributing to ACR20 and/or DAS28: tender and swollen joint counts, patient’s assessment of pain, patient’s and physician’s global assessments of disease activity, Functional Disability Index of the Health Assessment Questionnaire (HAQ-DI), ESR and CRP.

c: Safety laboratory includes biochemistry, hematology and differential cell count; urinalysis includes a pregnancy test for women of childbearing potential.

d: If patient experienced any gastrointestinal adverse event during course of study additional Hemoccult/guaiac tests must be performed.

e: At Visit 0 the study diary is only dispensed. There is no previous diary (from the last visit) to collect and review. At V4 a new diary is not dispensed, however the current diary (used since the last visit) is collected and reviewed. Patients complete the diaries every day during the study (each diary contains an additional 7 days, in case a visit is postponed).

f: If an AE is reported as ‘ongoing’ at Week 12, an additional follow-up will be performed at Week 16. If the ongoing AE at Week 12 involves a laboratory abnormality, an extra visit will occur at Week 16 for assessment of laboratory safety. If the ongoing AE at Week 12 does not involve a laboratory abnormality the patient will be followed up by telephone at Week 16.

Note:


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<th>Definition</th>
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</thead>
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<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALAT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
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<td>Alkaline Phosphatase</td>
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<td>Aspartate Aminotransferase</td>
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<td>Case Report Form</td>
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<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
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<td>C-reactive Protein</td>
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<tr>
<td>DAS</td>
<td>Disease Activity Score</td>
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<td>Disease Modifying Anti-Rheumatic Drugs</td>
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<td>Ethics Committee</td>
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<td>Erythrocyte Sedimentation Rate</td>
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<td>European League Against Rheumatism</td>
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<td>Functional Assessment of Chronic Illness Therapy - Fatigue</td>
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<tr>
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<td>Food and Drug Administration</td>
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<td>Good Clinical Practice</td>
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<tr>
<td>HAQ-DI</td>
<td>Functional Disability Index of the Health Assessment Questionnaire</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate-Release</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
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<tr>
<td>MR</td>
<td>Modified-Release</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
</tr>
<tr>
<td>PP</td>
<td>Per-protocol</td>
</tr>
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<td>RA</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SGOT</td>
<td>Serum Glutamic Oxaloacetic Transaminase (ASAT)</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum Glutamic Pyruvic Transaminase (ALAT)</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form 36 (Quality of Life)</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment Emergent Adverse Event</td>
</tr>
<tr>
<td>TNF(\alpha)</td>
<td>Tumor Necrosis Factor (\alpha)</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
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</table>
1. INTRODUCTION AND STUDY RATIONALE

1.1 BACKGROUND

Rheumatoid Arthritis (RA) is an inflammatory disease in which anti-inflammatory therapy plays an important role in the treatment of daily acute and painful symptoms. In addition, long-term failure to effectively control inflammation leads to bone and joint destruction, which cause irreversible cartilage damage and persistent disability.

Early morning symptoms, such as morning stiffness of the joints, are characteristic symptoms of RA. Morning stiffness of at least one hour in duration is required for the diagnosis of RA according to the “Guidelines for the Management of Rheumatoid Arthritis; Update 2002” (American College of Rheumatology [ACR] Subcommittee on Rheumatoid Arthritis Guidelines - 2002). The typical circadian rhythm of symptoms is well established, and was confirmed by objective measurements of joint stiffness and grip strength decades ago (Harkness et al. 1982). Nevertheless, despite the modern multifaceted standard treatments, including the so-called biologicals, morning symptoms still present a medical need today.

Glucocorticoids have been used in the treatment of RA since 1948, mainly because of their ability to relieve symptoms such as joint stiffness and joint pain but also because they slow down disease progression. Anti-inflammatory properties include the inhibition of interleukin-6 (IL-6) synthesis. IL-6 is one of the pro-inflammatory cytokines thought to play a major role in the pathogenesis of RA. The glucocorticoids most widely used today, such as prednisolone, have a short half-life of 2-3 hours and are usually given in the morning in order to minimize the disturbance of the physiological control of the endogenous adrenal steroid release cycle. The concept of low-dose corticoid therapy in the treatment of RA is well established nowadays, and its safety and effectiveness has been confirmed by several clinical trials (Kirwan 1995, van Everdingen et al. 2002, Wassenberg et al. 2005).

The circadian rhythm of disease activity in RA has no obvious explanation but the apparent diurnal variation of inflammatory processes might be triggered by circadian variation of plasma levels of cortisol (Harkness et al. 1982) and other endogenous factors (Cutolo et al. 2003, Bellamy et al. 2002). IL-6 plasma concentrations show a different pattern in healthy subjects compared to patients with RA. In healthy subjects (and in patients with non-arthritic diseases), IL-6 concentrations are very low (below 10 pg/mL) and peak at 4:00 a.m. (Sothern et al. 1995). In contrast, in patients with RA the serum concentrations of IL-6 show a marked rise – above ten-fold – in the early morning hours (Arvidson et al. 1994). This rise in IL-6 is significantly diminished by treatment with glucocorticoids, even when the conventional scheme of drug administration at 7:00–8:00 a.m. in the morning is being used. Providing appropriate plasma drug levels immediately prior to the circadian inflammatory flare-up was thought to enhance the safety and effectiveness of low dose glucocorticoid therapy (Harkness et al. 1982) and was confirmed by Arvidson et al. (1994).
The observations of the circadian rhythms of disease activity and proinflammatory cytokine levels led Arvidson and colleagues to administer prednisolone at night in order to suppress the early morning increase of IL-6. Taking into account an absorption period of 1–2 hours for the drug and a similar time interval for the establishment of full therapeutic activity, an intake at 2:00 a.m. was deemed optimal to achieve a maximum effect at 5:00 a.m. This hypothesis was tested in 26 patients with RA (Arvidson et al. 1994), who were on treatment with recommended standard anti-rheumatic drugs but treatment-naïve as far as glucocorticoids were concerned. These patients were randomly allocated to two groups of 13 patients for drug intake either at night (2:00 a.m.) or at 7:30 a.m. in the morning.

The evaluation of clinical and laboratory activity parameters revealed that the administration of low doses of prednisolone at 2:00 a.m. had favorable effects over standard 8:00 a.m. administration on all activity parameters. Improvements in the 2:00 a.m.-treatment group were statistically significant: duration of morning stiffness (P < 0.001), joint pain (P < 0.001), Lansbury index (P < 0.001), Ritchie index (P < 0.001), and morning serum concentrations of IL-6 (P < 0.01). The other study group showed minor but still significant effects on morning stiffness (P < 0.05) and circulating concentrations of IL-6 (P < 0.05). Modest but similar improvements of C-reactive protein, serum amyloid protein A, and erythrocyte sedimentation rate (ESR) were seen in both study groups. The authors concluded from these data that low doses of glucocorticoids improve acute RA symptoms if administration precedes the period of circadian enhancement of IL-6 synthesis and the flare-up of inflammatory activity.

Therefore, these observations led to the development of a modified release (MR) formulation of prednisone (Lodotra®), because a perfect disease-matched timing of the release of the drug may further reduce the doses needed to achieve the expected clinical benefit and to minimize the known side effects of long-term administration of glucocorticoids. In contrast to the marketed drug, this new pharmaceutical formulation can be conveniently taken by patients at bedtime (around 10 p.m.). After dissolution of the coating (after approximately 4 hours), unchanged prednisone is released and the subsequent pharmacokinetic behavior is identical to standard immediate-release prednisone.

A negative, depressing effect on the hypothalamic-pituitary-adrenal axis by this night-time application is not expected in the applied dose range of prednisone (La Rochelle et al. 1993). The rationale for night-time application of glucocorticoids to counteract the circadian early morning flare-up of pro-inflammatory cytokines has also been supported by recent publications on IL-6 and other cytokines (Choy et al. 2002). Furthermore, evidence of anti-rheumatic effects of anti-tumor necrosis factor α (TNFα) agents and IL-1 receptor antagonists is accumulating in the scientific literature (Kary et al. 2003).

The efficacy of Lodotra® in patients with active RA was investigated in a single, pivotal, randomized, double-blind, active-controlled, parallel-group phase III study. The study was specifically designed to compare the efficacy and safety of Lodotra® given in the evening with standard immediate release (IR) prednisone (Decortin, Merck KGaA) given in the morning at 08:00 over a period of 12 weeks. The patient population had long-standing disease and were pretreated with a combination of low-dose glucocorticoids and disease
modifying anti-rheumatic drugs (DMARDs). After 12 weeks of treatment, Lodotra® showed a statistically and clinically significant reduction in the duration of morning stiffness compared to standard IR prednisone. Furthermore, a decrease in morning plasma levels of IL-6 was observed in the Lodotra® group but not in the standard comparator group. There were no clinically meaningful treatment differences in any of the other secondary variables. Negative effects of the change in timing of prednisone administration were not observed in this study; there were no clinically relevant differences between the treatment groups in quality of sleep or recurrence of stiffness during the day (Buttgereit et al. 2008).

Lodotra® therefore represents an innovative prednisone formulation that provides all the benefits of standard IR prednisone but has the additional, clinically important advantage of reduced morning stiffness combined with a convenient dosing regimen.

1.2 RATIONALE

Patients with RA, whose symptoms are not adequately controlled with disease modifying anti-rheumatic drugs (DMARDs) may require additional therapy. The addition of low-dose, MR prednisone (Lodotra®) as additional therapy may provide patients, not only with the well known benefits of glucocorticoid therapy, but may also provide the additional benefit of reduced duration of morning stiffness and reduced levels of the pro-inflammatory cytokine IL-6 (Arvidson et al. 1997). Consequently, the aim of this study is to assess the efficacy and safety of 5 mg Lodotra® administered in the evening compared with placebo in this patient population.

During this study, all patients will be treated with a standard therapy of DMARDs. On top of this therapy, MR prednisone or placebo will be added. No medications will be withdrawn for the purpose of this study. Placebo was chosen as a comparator in order to establish the efficacy and safety (adverse event [AE] profile) of Lodotra® in this study population. The benefit risk ratio of the study design is considered favorable because (i) throughout the study, all patients receive standard DMARD therapy for their RA (ii) a 2:1 randomization was chosen to minimize the amount of patients receiving placebo treatment and (iii) patients with a deterioration of their disease will be withdrawn from the study.

This study will be conducted in compliance with the protocol and with the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) and applicable regulatory requirements.
2. **STUDY OBJECTIVES**

2.1 **PRIMARY OBJECTIVES**

The primary objective of this study is to evaluate if 12 weeks of treatment with 5 mg Lodotra® administered in the evening is superior to placebo in terms of the ACR20 responder rate.

2.2 **SECONDARY OBJECTIVES**

The key secondary objective of this study is to evaluate if 12 weeks of treatment with 5 mg MR prednisone (Lodotra®) administered in the evening is superior to placebo in terms of the relative reduction of morning stiffness.

Additional secondary objectives of this study are to compare 12 weeks of treatment with 5 mg Lodotra® administered in the evening with placebo in terms of:

- Efficacy:
  - Disease Activity Score (DAS)28 score
  - European League Against Rheumatism (EULAR) response criteria
  - Morning stiffness
    - Absolute reduction of duration of morning stiffness
    - Severity of morning stiffness
    - Reoccurrence of stiffness during day
  - Individual ACR20 and DAS28 criteria:
    - Tender joint count (ACR20 and DAS28)
    - Swollen joint count (ACR20 and DAS28)
    - Patient’s assessment of pain (ACR20) – assessed using 100mm visual analogue scale (VAS)
    - Patient’s global assessment of disease activity (ACR20 and DAS28) – assessed using 100mm VAS
    - Physician’s global assessment of disease activity (ACR20) – assessed using 100mm VAS
    - Functional disability index of the Health Assessment Questionnaire (HAQ-DI; ACR20)
    - ESR (ACR20 and DAS28) and C-reactive protein (CRP) (ACR20) as acute-phase reactants
  - Requirements for additional analgesics
Occurrence of pain in morning and evening
Inflammatory cytokines (IL-6 and TNFα)

- Quality of life:
  - HAQ-DI (as part of ACR20)
  - Short Form 36 (Quality of Life; Short Form [SF]-36)
  - Fatigue (Functional Assessment of Chronic Illness Therapy- Fatigue [FACIT-F])

- Safety:
  - AEs
  - Standard laboratory (hematology and biochemistry) parameters
  - Physical examination findings including assessment of vital signs (blood pressure, heart rate, body weight)

For definitions of the above see Section 10.1.

3. STUDY DESIGN, DURATION AND DATES

3.1 STUDY DESIGN

This is a randomized multi-center, double-blind, parallel-group, placebo-controlled 13 week study comparing evening administration of 5 mg Lodotra® to placebo in patients with RA. It is planned to randomize a total of 294 patients in 40 to 45 centers in North America and Europe. Approximately 350 patients will be enrolled (at Visit 0), with a minimum of 6 and a maximum of 28 patients at each center.

During the screening phase informed consent to participate will be obtained (at Visit 0) and the eligibility of the patient for enrollment will be assessed and documented. The patient must meet all inclusion and exclusion criteria at Visit 0 before receiving screening medication, and must also meet all randomization criteria at Visit 1 before receiving Lodotra® or placebo. Patients not treated with a glucocorticoid for the 6 weeks prior to the screening visit (at Visit 0) will be eligible for inclusion. The single-blind screening phase will last for 1 week, and will include daily recording of duration of stiffness in the diaries prior to Visit 1 to calculate a robust baseline value (average of 7 daily values collected on days –7 to –1).

Before randomization, all patients will receive placebo on top of their standard medication for a 1 week baseline period. No medication will be withdrawn during this period, so patients will remain treated at all times during the study.

The double-blind phase of the study starts with randomized allocation of eligible patients to one of the two arms (Lodotra® or placebo) at Visit 1 (baseline; Week 0). Efficacy of Lodotra® (5 mg daily dose [1 × 5 mg tablet], evening administration) will be derived from
the comparison with placebo. Patients will be treated with blinded study medication on a fixed dose for 12 weeks. The double-blind phase will consist of four visits (Visit 1 to Visit 4; Weeks 0, 2, 6 and 12). After the double-blind treatment phase, patients should be switched to 5 mg immediate-release prednisolone and should be tapered down according to best practice, if applicable.

Overall duration of the study is planned to be one and a half years. The study is scheduled to start in 2008. The study data will be evaluated and reported as soon as the study data of all randomized patients are entered and validated in the database, and the database is locked.

A parallel group, placebo-controlled design is being used to establish the efficacy of the test product. As stated in the introduction; since the test product belongs to an already well-characterized pharmacologic class, a trial duration of three months is sufficient to establish efficacy for treatment of signs and symptoms of RA.

3.2 STUDY DURATION, DATES, AND END-OF-STUDY DEFINITION

The duration of this study for each patient will be a maximum of 13 weeks (including a 1-week screening period), with patient recruitment planned to last for 6-9 months, starting in early 2008 and finishing in late 2008. The study will end in late 2009 after the database has been locked. The actual overall study duration or patient recruitment period may vary.

4. SELECTION OF PATIENTS

4.1 NUMBER OF PATIENTS

As calculated in Section 10.5, approximately 350 patients will be enrolled in this study, in order to randomize 294 patients. This sample will be obtained from approximately 40 to 45 centers in North America and Europe. It is expected that each study site will enroll between 6 and 28 patients. No site will enroll beyond 28 patients without prior written approval from the Sponsor. Sponsor approval will be based on both consideration of the potential for statistical analysis impact and the quality of work performed to date by the site as assessed through monitoring or auditing. Enrollment into the screening or randomization phase of the study will be stopped when the anticipated or actual patient numbers have been achieved across all study sites.

4.2 RECRUITMENT ARRANGEMENTS

Investigators may enroll patients from their existing or incoming patients.
4.3 INCLUSION CRITERIA

At Visit 0
Diagnosis:

- Rheumatoid Arthritis (RA)

Patients meeting all of the following criteria at Visit 0 will be considered for enrollment into the study:

- Provide written informed consent
- Have a documented history of RA (sero-negative or sero-positive) in agreement with the ACR criteria, including the symptoms morning stiffness, joint pain, tender and swollen joints, inflammatory state with elevated ESR or CRP
- Be on DMARD treatment for RA for at least 6 months, with a stable dose for at least 6 weeks prior to the screening visit (Visit 0)
- Have duration of morning stiffness of at least 45 minutes
- Have swollen joint count of 4 or more out of 28
- Have tender joint count of 4 or more out of 28
- Aged 18 to 80 years
- Female patients of childbearing potential must be using a medically accepted contraceptive regimen
- Able to perform the required study procedures including handling of medication containers and diaries

4.4 RANDOMIZATION CRITERIA

At Visit 1
Patients must meet all of the following randomization criteria at Visit 1 to be eligible for randomization into the double-blind treatment period at the randomization visit:

- Symptomatic status required for inclusion:
  - Have duration of morning stiffness of 45 minutes or more (on at least 4 days within the last 7 days)
  - Have swollen joint count of 4 or more out of 28
  - Have tender joint count of 4 or more out of 28
- Adequate compliance in completing study diaries
- Medication compliance (± 1 tablet of the calculated tablet range)
- Negative Hemoccult/guaiac test
4.5 EXCLUSION CRITERIA

Patients presenting with any of the following will not be included in the study:

- Suffering from another disease, which requires glucocorticoid treatment, e.g. asthma, neurodermatitis
- Synovectomy within 4 months prior to study start
- Use of glucocorticoids (by any route) within 6 weeks prior to screening Visit 0
- Use of biologicals: TNFα inhibitor within 3 months prior to screening Visit 0, other compounds within 1 year prior to screening Visit 0
- Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation
- Pregnancy or nursing
- Participation in another clinical study (use of an investigational product) within 30 days preceding Visit 0
- Re-entry of patients previously enrolled in this trial
- Suspected inability or unwillingness to comply with study procedures
- Alcohol or drug abuse
- Requirement of nonpermitted concomitant medication
- Known hypersensitivity to prednisone or prednisolone
- Any contraindication for low dose prednisone treatment
- Significant renal impairment (serum creatinine > 150 µmol/L)
- Significant hepatic impairment (investigator’s opinion)
- Any uncontrolled concomitant disease requiring further clinical evaluation (e.g. uncontrolled diabetes, uncontrolled hypertension etc.)

Any deviation or change from the protocol, including the inclusion/exclusion criteria, must be approved in writing by the Sponsor and approved by the Institutional Review Board (IRB) or Ethics Committee (EC). In accordance with local regulations, the Sponsor may be required to notify local regulatory agencies.

A patient may not be enrolled nor randomized in this study more than once. A patient may repeat the screening phase once, only if gastrointestinal bleeding can be excluded by a gastroenterologist after the first Hemoccult/guaiac test was positive. No patients who have previously been treated with the investigational product will be enrolled in this study.
4.6 WITHDRAWALS

4.6.1 Withdrawal of patients

Patients must be withdrawn from the study (i.e. from any further study medication or study procedure) for the following reasons:

- At their own request
- If, in the investigator’s opinion, continuation in the study would be detrimental to the patient’s well-being
- Therapeutic failure requiring urgent additional medication
- Occurrence of AEs, if discontinuation of study drug is desired or considered necessary by the investigator and/or patient
- Occurrence of pregnancy
- Permanent requirement of non-permitted concomitant drug.
- Unblinding of the study drug for any reason
- Repeated (more than once) unreliability for keeping study appointments, i.e. > 3 days during double-blind phase

If a patient has failed to attend scheduled assessments in the study, the investigator must determine and document the reasons and the circumstances as completely and accurately as possible.

In case of premature discontinuation of the study by a patient, the investigations scheduled for the last visit should be performed, if possible. In any case, the case report form (CRF) section entitled “End of Study” must be completed.

If a patient discontinues the study prematurely they should be switched to 5 mg immediate release prednisolone and should be tapered down according to best practice, if applicable (see Section 5.2).

In all cases, the reason for and date of withdrawal must be recorded in the CRF and in the patient’s medical records. The patient must be followed up to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in Section 8.

As far as possible, all examinations scheduled for the final study day must be performed on all patients who receive the investigational product but do not complete the study according to the protocol.

The investigator must make every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient’s records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).
4.6.2 Replacement of patients

Patients will not be replaced.

4.6.3 Withdrawal of blood and urine samples (Europe only)

As stated in the informed consent form and according to national provisions, the patient may request all previously retained identifiable samples to be destroyed to prevent future analyses.

4.7 PATIENTS OF REPRODUCTIVE POTENTIAL

Female patients of childbearing potential (i.e., ovulating, pre-menopausal, not surgically sterile) must use contraceptive regimen during the study. The contraceptive method(s) chosen should be medically, culturally, and geographically acceptable as well as proven to have an acceptably low failure rate.

If a patient becomes pregnant while enrolled in the trial, the investigational product should be discontinued, and the patient withdrawn from the study. Further treatment should be addressed on a case-by-case basis with the treating physician and the investigator.

If pregnancy occurs, the investigator must contact the Sponsor immediately for further instruction. Both the detection and the outcome of the pregnancy must be reported to the Sponsor on special forms. All recommendations described in the drug information on glucocorticoid treatments during pregnancy and lactation have to be carefully considered.

If a female patient becomes pregnant during the trial, she must be followed up until the outcome of the pregnancy is known.
5. STUDY TREATMENTS

5.1 DETAILS OF STUDY TREATMENTS

<table>
<thead>
<tr>
<th>Visit</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
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<td>-1</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Tablets</td>
<td>20</td>
<td>20</td>
<td>20-20</td>
<td>20-20-20</td>
<td></td>
</tr>
</tbody>
</table>

5.1.1 Study medication

Study medication consists of MR prednisone tablets in one dose strength (i.e. 5 mg prednisone per tablet) and matching placebo tablets.

MR prednisone tablets consist of prednisone core tablets press coated with an inactive outer layer as special coating. Therefore, it has to be swallowed as a whole tablet and must not be broken in half or chewed. Dissolving of the tablets in a beverage before swallowing is also not permitted.

Size and shape of the tablets are identical. The tablets are round, cylindrical, 9 mm in diameter and 5 mm in height. There is no break line.

For this study 5 mg MR prednisone tablets and matching placebo tablets are available.

The MR prednisone tablets and the placebo tablets were manufactured by Skye Pharma, Lyon, France.

5.1.2 Packaging design

According to the double blind study design, all medication will be packed identically for both treatment groups (MR prednisone tablets or respective placebo tablets).
5.1.2.1 Bottles

Study medication is always packed in white round polyethylene containers (bottles) of 40 mL containing 20 tablets each. The push-fit tamper-evident caps are designed to ease the opening procedure for users with special needs. The cap has three fixation points on the top to enable opening assisted by a tool, for instance, a pen.

5.1.2.2 Visit bottles

Each visit bottle contains 20 tablets each. (1 bottle with MR prednisone 5 mg tablets or matching placebo tablets).

5.1.2.3 Screening boxes

1 screening box contains 12 bottles with 20 tablets each
5.1.2.4 Medication Boxes

1 medication box contains 6 visit bottles with 20 tablets each for visits 1, 2 and 3

![Diagram showing medication boxes for visits 1, 2, and 3]

5.1.3 Medication Dispensation

5.1.3.1 Medication for run in period (Visit 0 – 1 week)

- One bottle placebo will be dispensed to each patient at Visit 0 for a 7-day placebo run-in phase between Visits 0 and 1. The purpose of the placebo run-in is to enable an assessment of compliance with study medication and adequate completion of study diaries to be made at Visit 1 as part of the final decision on whether or not to randomize a screened patient to study treatment.

- **Visit 0 (Week -1):** 1 bottle
  - 20 placebo tablets matching MR prednisone 5 mg tablets

5.1.3.2 Medication for treatment period (Visit 1, 2 and 3)

Each patient will then receive study medication at Visit 1, 2 and 3 for the following 12 weeks treatment.

The following will be dispensed at:

- **Visit 1 (Week 0):** 1 bottle
  - 20 MR prednisone 5 mg tablets or matching placebo tablets

- **Visit 2 (Week 2):** 2 bottles, each containing
  - 20 MR prednisone 5 mg tablets or matching placebo tablets
Visit 3 (Week 6): 3 bottles, each containing
- 20 MR prednisone 5 mg tablets or matching placebo tablets

Medication will be packed for each patient and will contain sufficient medication for treatment during Weeks 0 – 12. A “medication box” will be prepared which will contain 6 visit bottles, one bottle given at Visit 1, two bottles given at Visit 2 and three bottles given at Visit 3.

All study medication has to be stored carefully at the study site. It has to be kept safely and separately from other drugs and must not to be exposed to direct sunlight or heat. For storage, study medication is to be kept in the range between 2-25°C/36-77°F). At the site the temperature must be monitored at least with min-max thermometer or equivalent.

5.2 DOSAGE SCHEDULE

5.2.1 Treatment during the screening phase

Patients will enter the screening phase on a stable DMARD treatment for RA for at least 6 weeks prior to screening. Stable disease must be documented during the screening period. According to the inclusion and exclusion criteria (Sections 4.3 and 4.4) study eligible patients must be in a state of disease such that no changes of doses or of concomitant medications are necessary during the screening phase (i.e. stable conditions for 1 week prior to Visit 1).

5.2.2 Treatment during the double-blind phase

After randomization (at Visit 1) all patients will receive a fixed dose of 5 mg Lodotra® or placebo (1 x 5 mg tablet). Study medication will be taken with or after the evening meal (if possible around 10 p.m. ± 30 minutes) and be swallowed unchewed with sufficient liquid to ensure optimum efficacy. If more than 2–3 hours have passed since the evening meal, it is recommended to take the tablets with a light meal or snack.

During the 12 weeks of the double-blind treatment phase dose changes of the study drugs are not permitted.

5.2.3 End of Treatment

If a patient is withdrawn from study medication for any reason (for example in the event of an AE) and at the end of the 12-week double-blind treatment phase, the patient must be switched to 5 mg immediate release prednis(lo)ne and should be tapered down according to best practice, if applicable (see Section 7.2.3). In general it is not advisable to withdraw glucocorticoids abruptly. A rapid reduction in dose or withdrawal from prednis(lo)ne might cause an increase in disease activity and severity of symptoms.
5.3 TREATMENT ASSIGNMENT AND RANDOMIZATION

The investigational product will be administered only to patients for whom appropriate written informed consent is obtained (see Section 11.3).

Each patient for whom informed consent is obtained will be assigned a unique patient number. This number will be four digits long. The first two digits will be the site number and the second two digits will be a unique patient identifier, assigned to the patient by the investigator, strictly in chronological order of enrolment (within each site). The unique 4-digit patient number will be used as the subject ID on the CRF and will be used to identify the patient throughout the study.

The randomization schedule will be generated by ICON. The randomization schedule will link sequential numbers to treatment codes allocated at random with a 2:1 (Lodotra® vs. placebo) randomization ratio. The randomization numbers will be blocked. Within each block, the same number of patients will be allocated to each of the two treatment groups. The block size will not be revealed. In addition, randomization to study medication will be balanced by investigational site.

The investigational product will be labeled with a 3 digit medication number (=randomization number).

The next patient eligible for randomization will receive the lowest available medication number within the study site. Each patient must be given only the study treatment he was allocated to. The investigator will document the medication number in the CRF.

Patients withdrawn from the study retain their patient number and their medication number, if already provided. New patients must always be allotted a new patient number and, if applicable, a new medication number.

Study treatments are blinded and the randomization schedule and the allocation to treatment groups will not be known to the investigator, the Sponsor or any other person involved in the conduct of the study until completion of the study, except in the case of an emergency. Each investigator will be provided with a set of emergency code break envelopes corresponding to the medication numbers relevant for the study site. Each envelope will contain the treatment to which the individual medication number was allocated. This information will not be legible unless the envelope has been opened. An envelope may only be opened in the case of an emergency, i.e. if it is necessary for medical reasons to know which of the study treatments the specific patient has received. The investigator must document the reason for breaking the code. The signed and dated letter will be filed in the investigator’s site file.

The randomization schedule will be kept by the randomization code administrator who is independent from the study team. A copy of the randomization schedule will be provided to the drug supplier responsible for packaging the investigational products.
5.4 LABELING OF STUDY MEDICATION

The investigational medicinal product will be labeled in accordance with the principles of Good Manufacturing Practice.

Information relating to administration is included on the labels of the bottles. Additional statements will be printed on the label(s) as required by local regulations. All bottles and boxes will bear labels with texts printed in local languages.

The label on the “visit bottle” has two parts, the tear-off part will be taken off the bottles when these are distributed to a patient. The slips should be attached to the appropriate spaces in the CRFs to document the correct distribution of the study medication to the patients as they are randomized.

From the documentation of the study medication, it will be possible to retrace the composition and pharmaceutical quality according to the current GMP guidelines.

Details of emergency unblinding procedures are given in Section 9.2.

5.5 SUPPLIES AND ACCOUNTABILITY

The investigator or pharmacist will record and acknowledge receipt of all shipments of the investigational product and document the condition of each shipment. The investigational products must be kept in a locked area with restricted access. The investigational products must be stored and handled in accordance with the manufacturer’s instructions. The investigator is responsible for maintaining documentation showing the amount of investigational product provided to the investigational site, and dispensed to and collected from each study patient. Discrepancies in investigational product accountability must be explained and documented. An inventory of investigational products will be maintained. The monitor is responsible for verifying the investigator’s documentation on receipt, use and return of investigational products. The monitor will check drug accountability at sites on an ongoing basis from the start of the study. The monitor will prepare a final report of the accountability of the investigational product for filing in the investigator file. Thereafter, the medication may be destroyed.

5.6 COMPLIANCE

Patients will be instructed to return all unused medication and all used packaging materials to the investigational site at each visit.

Patients’ compliance to study medication will be checked by the investigator or their designee(s) and documented in the CRFs (tablet count, timing of doses verified according to diary entries).
At randomization, a patient is regarded as compliant if the consumption of study medication for the screening period is ± 1 tablet of his or her calculated tablet range.

Furthermore, during the double-blind phase the correct timing of the study medication’s administration is of crucial importance. Study medication should be taken with or after the evening meal (if possible around 10 p.m. ± 30 minutes) and be swallowed unchewed with sufficient liquid to ensure optimum efficacy. If more than 2–3 hours have passed since the evening meal, it is recommended to take the tablets with a light meal or snack.

Time of intake is to be recorded in the patient’s diary and should be around 10 p.m. (± 30 minutes). Patients who deviate from this time will be carefully advised as to the importance of compliance, and taking the study medication at the required time.

Adherence of the patients to the visit schedule will also be assessed. This is regarded as sufficient if deviations do not exceed ± 3 days and medication compliance is maintained. Larger deviations should be corrected at subsequent visits to adhere to the overall treatment duration during the double-blind phase of 12 weeks (Visits 1–4).

6. PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

6.1 PRIOR AND CONCOMITANT ILLNESSES

Additional illnesses present at the time informed consent is given are regarded as concomitant illnesses and must be documented in the CRF. Relevant past illnesses must also be documented in the CRF.

Illnesses first occurring or detected during the study, and worsening of concomitant illnesses during the study, are to be regarded as AEs and must be documented as such in the CRF (see Section 8).

6.2 PRIOR AND CONCOMITANT TREATMENTS

All treatments taken by the patients on entry to the study or at any time during the study in addition to the investigational product, are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

Relevant previous treatments taken within 30 days before the study must also be documented in the CRF.

During the screening phase (Visit 0 to Visit 1) patients must continue with their previous therapies so as to maintain stable conditions. If they have been applying routine therapies of a physical nature, such as rinsing their hands with warm water to enhance relief from stiffness, they should proceed in the same way during the study.
Regular treatment with other DMARDs and non-steroidal anti-inflammatory drugs (NSAIDs), should remain constant during the double-blind treatment phase. The same applies to physical therapy. Relevant changes subsequent to disease progression (e.g. AEs) have to be documented in the AE and concomitant medication sections of the CRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient’s welfare and are unlikely to interfere with the investigational products, they may be given at the discretion of the investigator and recorded in the CRF.

The following concomitant treatments are permitted during this study: NSAIDs and DMARDs (excluding any biologicals) only if they were started before the study (see Section 4.3) and on a stable dose. Investigators should advise the patients that in the event of an acute exacerbation of pain they should use a non-anti-inflammatory and non-antibiotic painkilling drug, preferably paracetamol/acetaminophen. Any such event and the consumption of any analgesics must be documented by the patients in their diaries (yes or no) as well as by the investigator in the CRFs (detailed documentation in the AE and concomitant medication sections). Other drugs for the treatment of concomitant diseases are allowed, however their dosage should be kept constant throughout the study.

The following concomitant treatments are not permitted during this study:

- Glucocorticoids other than the study medication
- Intra-articular injections and synoviorthesis
- Biologicals
- Initiation of DMARD therapy
- Initiation of NSAID therapy

7. STUDY PROCEDURES AND SCHEDULE

7.1 OVERVIEW OF DATA COLLECTION

Ethnic differences may affect a medication’s safety, efficacy, dosage, and dose regimen (ICH Topic E5: Ethnic factors in the Acceptability of Foreign Clinical Data). Each patient’s race will be recorded and stored in the database for this study in order to facilitate the detection of such ethnic differences.
7.2 DESCRIPTION OF STUDY VISITS

An overview of the study schedule is provided on page 12.

7.2.1 Screening

Visit 0 (Week -1)

Patients should attend the investigator’s office between 8 and 10 a.m. and the investigator will:

- Discuss the patient’s possible participation in the study and its implications
- Give the patient a Patient Information Leaflet/Informed Consent Form

If a patient is willing to participate, the investigator will:

- Ask the patient to sign and date an informed consent form
- Check inclusion and exclusion criteria
- Note the demographic and baseline characteristics, i.e. date of birth, gender, ethnicity (Hispanic or Latino, Not Hispanic or Latino) and race (American Indian/Alaska Native, Asian, Black / African American, Native Hawaiian or Other Pacific Islander, Caucasian or White, Other)
- Assess the patient’s medical history, including treatments (previous and current medications)
- Perform a physical examination including assessment of vital signs (blood pressure, heart rate, body weight) and height
- Assess the rheumatoid disease status by means of the following factors contributing to the ACR20 and/or DAS28
  - Tender joint count (ACR20 and DAS28)
  - Swollen joint count (ACR20 and DAS28)
  - Patient’s assessment of pain (ACR20; documented in the CRF)
  - Patient’s global assessment of disease activity (ACR20 and DAS28)
  - Physician’s global assessment of disease activity (ACR20)
  - HAQ-DI (ACR20)
  - Collect venous blood samples for assessment of acute-phase reactants:
    - ESR measured in local laboratories (ACR20 and DAS28)
    - CRP measured in central laboratory (ACR20)
• Collect venous blood samples for central laboratory assessments of:
  - Safety laboratory parameters
    - Hematology
    - Biochemistry
    - Differential cell count
  - Inflammatory cytokines (IL-6 and TNFα)

• Dipstick urinalysis (central laboratory) for all patients and a pregnancy test for women of child-bearing potential

• Give the patients a diary with precise instructions as to how it should be used and completed by the next visit

• Distribute sufficient study medication (placebo) until next visit (see Section 5.1)
  - Instruct the patients how to compose their daily 5 mg dose using 5 mg tablets
  - Attach medication labels from the medication box to the respective CRF page
  - Instruct the patients on the importance of taking the study medication exactly as described, i.e. in the evening at 10 p.m. (± 30 minutes) together with or after some light food
  - Patients should be ‘blind’ to the fact that they will receive placebo for the first week
  - Instruct the patient to return any unused study medication and all used packaging at the next visit

• Distribute a Hemoccult/guaiac test kit with precise instruction how it should be used. Instruct patient to perform the test within 5 days of the next scheduled visit. Instruct patient to return the Hemoccult/guaiac test at the next visit.

• Fix a date and time (between 8 and 10 a.m.) for the next appointment (Visit 1). The interval between Visit 0 and Visit 1 will be 1 week

Details of any patient who is screened but not enrolled will be entered on a screening log.

7.2.2 Study visits

Visit 1 (Week 0; start of double-blind treatment phase)

Patients should attend the investigator’s office between 8 and 10 a.m. and the investigator will:

• Collect the current diary and review the diary entries to ensure that it has been used correctly
Collect the Hemoccult/guaiac test samples. Develop the test samples according to the guideline provided by the central laboratory and evaluate the test. Provide an extra test kit and advise patient to contact the site when experiencing any gastrointestinal AE.

Assess patient’s compliance by reviewing the:
- Medication containers (i.e. tablet count of returns)
- Diary entries relating to morning stiffness, stiffness during day (while performing routine activities), time of medication intake, and analgesics (painkillers)

Perform an assessment of vital signs (blood pressure, heart rate, body weight)

Confirm stable disease conditions by performing assessments required to calculate rheumatoid disease activity in terms of ACR diagnostic criteria and DAS28
- Tender joint count (at least 4 tender joints)
- Swollen joint count (at least 4 swollen joints)
- Patient’s assessment of pain
- Patient’s global assessment of disease activity
- Physician’s global assessment of disease activity
- HAQ-DI
- Collect venous blood samples for assessment of acute-phase reactants:
  - ESR measured in local laboratories
  - CRP measured in central laboratory

Assess concomitant use of medications (e.g. paracetamol)

Ensure completion of quality of life questionnaire (SF-36) and fatigue (FACIT-F) questionnaire by the patient

Allocate eligible patients to randomized treatments and fax confirmation of randomization

Give the patients their next diary with precise instructions as to how it should be used and completed by the next visit

Distribute sufficient randomized study medication until next visit (see Section 5.1)

Instruct the patient to return any unused study medication and all used packaging at the next visit

Document incidences and types of AEs in the CRF

Fix a date and time (between 8 and 10 a.m.) for the next appointment (Visit 2)
Visits 2 and 3 (Weeks 2 and 6)

Patients should attend the investigator’s office between 8 and 10 a.m. and the investigator will:

- Assess patient’s compliance by reviewing the:
  - Medication containers (i.e. tablet count of returns)
  - Diary entries relating to morning stiffness, stiffness during day (while performing routine activities), time of medication intake, and analgesics (painkillers)
- Collect their current diary and review the diary entries to ensure that it has been used correctly
- Perform an assessment of vital signs (blood pressure, heart rate, body weight)
- Perform assessments required to calculate rheumatoid disease activity in terms of ACR diagnostic criteria and DAS28
  - Tender joint count
  - Swollen joint count
  - Patient’s assessment of pain
  - Patient’s global assessment of disease activity
  - Physician’s global assessment of disease activity
  - HAQ-DI
  - Collect venous blood samples for assessment of acute-phase reactants:
    - ESR measured in local laboratories
    - CRP measured in central laboratory
- Assess concomitant use of analgesics (paracetamol/acetaminophen) and record any changes in concomitant medication in the CRF
- Document incidences and types of AEs in the CRF
- Dispense sufficient randomized study medication until next visit (see Section 5.1)
- Instruct the patient to return any unused study medication and all used packaging at the next visit
- Give the patients their next diary with precise instructions as to how it should be used and completed by the next visit
- At Visit 3: Distribute a Hemoccult/guaiac test kit with precise instructions on how it should be used. Instruct patient to perform the test within 5 days of the next scheduled visit. Instruct patient to return the Hemoccult/guaiac test at the next visit. Two weeks prior to the next scheduled visit contact and remind patient to collect stool samples
• Fix a date and time (between 8 and 10 a.m.) for the next appointment, if necessary

7.2.3 End of treatment

Visit 4 (Week 12; end of double-blind phase)

Patients should attend the investigator’s office between 8 and 10 a.m. and the investigator will:

• Assess patient’s compliance by reviewing the:
  - Medication containers (i.e. tablet count of returns). The investigator will ensure complete documentation of drug accountability during the study
  - Diary entries relating to morning stiffness, pain, stiffness during day (while performing routine activities), time of medication intake, and analgesics (painkillers)

• Collect the current diary and ensure that the complete set of diary booklets have been returned

• Perform a physical examination including assessment of vital signs (blood pressure, heart rate, body weight)

• Perform assessments required to calculate rheumatoid disease activity in terms of ACR diagnostic criteria and DAS28
  - Tender joint count
  - Swollen joint count
  - Patient’s assessment of pain
  - Patient’s global assessment of disease activity
  - Physician’s global assessment of disease activity
  - HAQ-DI
  - Collect venous blood samples for assessment of acute-phase reactants:
    - ESR measured in local laboratories
    - CRP measured in central laboratory

• Check concomitant use of analgesics (paracetamol/acetaminophen) and record any changes in concomitant medication in the CRF

• Document incidences and types of AEs in the CRF

• Ensure completion of a quality of life questionnaire (SF-36) and a fatigue (FACIT-F) questionnaire by the patient

• Collect venous blood samples for central laboratory assessments of
  - Safety laboratory parameters
- Hematology
- Biochemistry
- Differential cell count
- Inflammatory cytokines (IL-6 and TNFα)

- Dipstick urinalysis (central laboratory) for all patients and a pregnancy test for women of child-bearing potential (Section 7.3.2.2)
- Collect Hemoccult/guaiac test samples. Develop the test samples according to the guideline provided by the central laboratory and evaluate the test
- Collect unused double-blind medication
- Provide information on alternative treatment options. Switch patients to 5 mg immediate release prednisolone. Prednisolone should be tapered down according to best practice, if applicable.

7.3 METHODS OF ASSESSMENT

7.3.1 Efficacy assessments

Efficacy data is based on:
- Individual ACR20 criteria (as outlined in Section 2.2)
- Individual DAS28 criteria (as outlined in Section 2.2)
- EULAR response criteria
- Laboratory assessments of acute phase reactants (ESR, CRP, IL-6 and TNFα)
- Diary entries relating to morning stiffness, stiffness during the day (while performing routine activities), time of medication intake, and analgesics (painkillers)

7.3.1.1 Patient's and physician’s global assessment of disease activity

With these tools the actual state of disease is assessed as it is captured on the actual day of the visit, i.e. no recall or summary state of disease is asked for.

Disease activity will be assessed by both patients and physicians using a 100 mm VAS with the endpoints 0 = not active at all and 100 = extremely active. Patients and physicians will mark points on the scale.

7.3.1.2 Patient’s assessment of pain

The actual state of pain is assessed during the visit, i.e. no recall or summary state of disease is asked for.
Maximum intensity of pain will be documented and intensity will be assessed by marking the respective value on a 100 mm VAS (with the endpoints 0 = no pain at all and 100 = very intensive pain).

7.3.1.3 Tender joint count

At every visit, investigators will inspect the patient’s joints. A 28 joint graph will be used for the documentation of the number of tender and swollen joints (an example will be provided in Appendix II).

The following 28 joints (14 left, 14 right) will be assessed for tenderness: shoulder, elbow, wrist (radiocarpal, carpal and carpometacarpal are collectively designated wrist), metacarpophalangeal I–V, thumb interphalangeal, proximal interphalangeal II–V, knee [5, 6, 9]. The investigator applies pressure to each joint and then moves it through a full range of motion. The tender joint count represents the number of joints in which pain is reported after either maneuver.

7.3.1.4 Swollen joint count

The investigator also assesses the same 28 joints (listed above) for swelling. The swollen joint count represents the number of joints in which there is synovial fluid and or soft tissue swelling, but not if bony overgrowth is found.

7.3.1.5 Functional disability index of the Health Assessment Questionnaire (HAQ-DI)

Generally accepted validated questionnaires will be the basis for the patients' self-assessment of their health status.

The HAQ-DI includes eight blocks of questions covering difficulties when performing simple daily activities, such as personal hygiene (washing, and dressing or undressing), mobility domestic and outdoors (walking, mounting steps, going shopping, carrying things), as well as intake of food or drink and, the handling of tools used in everyday life.

- The answers are to be given by marking tick-boxes at each visit to indicate the degree of difficulty on a 4 point grading system, e.g.:
  - 0 = none
  - 1 = some difficulty
  - 2 = great difficulty
  - 3 = not able to perform at all

- Furthermore, the use of mechanical aids and the need for helpers is queried

The investigator will check for plausibility and completeness of entries, without influencing the patients in their assessments.
7.3.1.6 Functional assessment of chronic illness therapy-fatigue (FACIT-F)

The FACIT-F questionnaire is used to assess the affect of patient’s fatigue on their daily activity and function. It is a 13 item questionnaire which is completed by the patient, and each answer is given according to the following 5 point grading system:

- 0 = not at all
- 1 = a little bit
- 2 = somewhat
- 3 = quite a bit
- 4 = very much

The investigator will check for plausibility and completeness of entries, without influencing the patients in their assessments.

7.3.1.7 Laboratory assessments (ESR, CRP, IL-6 and TNFα)

Blood sampling for the assessment of the laboratory efficacy parameters must be done at the same time for all visits. These parameters are:

- ESR will be assessed at local laboratories using routine local standard methods and equipment. ESR will be assessed (in mm/h) by measuring the sedimentation rate in the first hour after withdrawal of blood at each visit. These data will be used for the assessment of the Disease Activity Scores (DAS) and ACR20
- CRP (mg/L) will be analyzed from 1 mL serum by a central laboratory and will be used for the determination of ACR20
- Interleukin-6 (IL-6; pg/mL) and TNFα will be measured, and the blood samples for the determination of these parameters will be processed and stored according to protocols provided by the central laboratory

Investigators will not be notified of the final test results (CRP, IL-6 and TNFα) during the double-blind phase of the study. After database lock and unblinding of the medication, investigators will receive CRP-, TNFα- and IL-6 data of their study patients (a copy of the laboratory reports will also be provided to the monitors to safeguard correct filing in the patient and site files).

The central laboratory will be responsible for all laboratory logistics and analyses (except ESR). Detailed instructions about the handling of blood samples, storage until dispatch and transportation particulars will be described in a special laboratory manual, provided by the central laboratory.
7.3.1.8 Hemoccult/Guaiac Tests

Hemoccult/guaiac tests must be performed prior to randomization at Visit 0 and prior to the end of treatment at Visit 4. In the case patients experiencing any gastrointestinal adverse events, additional Hemoccult/guaiac tests must be performed.

Screening phase/Randomization

At Visit 0 the investigator will provide the Hemoccult/guaiac test kit to the patient with precise instructions on the correct handling of the test kit. In addition, patients will receive a test instruction sheet. Patients will be reminded to return the test kit at the next visit. Patients should perform the test during the screening phase within 5 days prior to the next scheduled visit.

At Visit 1, prior to randomization, the investigator will collect the test samples. The investigator will be responsible for developing the test samples according to the guidelines provided by the central laboratory. The results of the tests should be evaluated and documented by the investigator.

Patients with a positive test will be advised to contact a gastroenterologist. If gastrointestinal bleeding can be excluded by the gastroenterologist, the patient may repeat the screening phase. If the Hemoccult/guaiac test result is again positive, the patient must not be randomized.

At Visit 1, an extra test kit will be provided to the patient.

During treatment phase and end of study

Patients will be advised to contact the site when experiencing any gastrointestinal AE. Under direction of the investigator, the patient must be instructed to collect new samples with the extra test kit provided, and return it to the site.

At Visit 3, patients will receive a new Hemoccult/guaiac sample kit. Two weeks prior to Visit 4, the site should contact and remind the patient to collect samples and return the test kit at the next visit.

At Visit 4, the test samples will be collected and developed by the investigator. Results will be documented and evaluated by the investigator.

If, at the end or during the study, the Hemoccult/guaiac test is positive, the patient must consult a gastroenterologist, and if gastrointestinal bleeding cannot be excluded, a gastrointestinal endoscopy must be performed. Medical reports of the gastroenterologist will be blinded and forwarded to the Sponsor.

The central laboratory will be responsible for distributing Hemoccult/guaiac test kits to the site. Test results will be evaluated locally. Detailed instructions about the handling of the
Hemoccult/guaiac test will be described in a special laboratory manual, provided by the central laboratory.

7.3.1.9 Diary

Diary cards for the double-blind phase will be created in the form of booklets. Patients will be instructed to enter their data twice daily, i.e. in the mornings always immediately after morning stiffness has abated as much as is needed to perform these procedures. In the evenings occurrence of pain and episodes of recurring stiffness during the day have to be recalled and entered following the respective questionnaire. Further entries concern the medication intake.

Parameters to be entered by the patients daily are as follows:

- Procedures to be performed or data to be entered in the mornings:
  - Wake-up time
  - Stiffness of joints? (yes/no)
    - If yes, daily severity of morning stiffness (VAS)
    - If yes, time of resolution of morning stiffness
  - Pain at wake-up time

- Procedures to be performed in the evenings:
  - Pain during the day? (yes/no)
    - If yes, maximum intensity of pain during the day (no pain at all - very intense pain [VAS])
  - Painkillers taken during the last 24 hours? (yes/no)
    - If yes,
    - Time when painkiller was taken
    - Type (preferably paracetamol)
    - Dose
  - Recurrence of stiffness? (yes/no)
  - Time of medication intake in the evening

The patients have to present their diaries to the investigator at every visit. The investigator will review the diary at every visit, starting with the assessment of the suitability of the patient for enrollment at Visit 1 (data on 7 days have to be available for assessment of baseline). Furthermore, a regular review of the diary is mandatory for the detection of errors with the medication intake times, missing entries, lack of compliance etc.
Furthermore, the investigator has to check the usage of concomitant medication (analgesics) as entered in the diary.

After the review of the entries for plausibility and completeness, the investigator will collect the first (original) pages of the visit sets for data management. The investigator is responsible for the correct identification of the collected pages, with patient number, date and initials (no names, to safeguard data protection).

Correct and complete data entry into the diaries by the patients will allow the evaluation of the following variables by data management:

- Reduction in and duration of morning stiffness (minutes). This will be determined from the following information entered in the diary:
  - Waking-up time
  - Stiffness? (yes/no)
  - Time of resolution of morning stiffness
- Recurrence of stiffness during the day? (yes/no)
- Compliance of medication intake time for medication (24 hour clock)
- Requirements for additional analgesics (yes/no) and analgesic dose per day (mg)
- Concomitant medication changes (yes/no)*

* Type of drug, dose and reason for changes have to be documented in the CRF page relating to concomitant medication and, if applicable, an AE has to be documented in the AE or serious adverse event (SAE) section of the CRF, and or notified by SAE Fax to ICON (see Section 8).

7.3.2 Safety assessments

7.3.2.1 Adverse events

Incidences and types of AEs will be recorded in the CRF from signing of informed consent to end of study, as described in Section 8.

7.3.2.2 Laboratory measurements

Venous blood samples will be obtained for the assessment of safety parameters. Samples may be withdrawn from the patient in a fasted or non-fasted state. However all visits should occur at the same time (i.e. between 8 a.m. and 10 a.m.) and the patient should always be in the same state.

Laboratory parameters will be measured both in local laboratories (ESR) and in a central laboratory (hematology, urinalysis, CRP, IL-6, TNFα and serum chemistry; see
Section 7.3.1.7). The investigators will be immediately notified of central laboratory test results so as to monitor the patient’s state of health. Laboratory assessments required for general safety monitoring of the patients are as follows:

**Local laboratories of the individual centers**
- ESR will be evaluated as an efficacy variable (Section 7.3.1.7)

**Central Laboratory**
- Hematology (EDTA-blood):
  - Hemoglobin (g/dL)
  - Red blood cell count
  - White blood cell count
  - Platelet count
- Urinalysis:
  - Dipstick routine test for protein, glucose, erythrocytes
  - Urine CTX
  - Pregnancy test (women with childbearing potential only)
- Serum chemistry:
  - Sodium (Na+; mmol/L)
  - Potassium (K+; mmol/L)
  - Calcium (Ca++; mmol/L)
  - Chloride (Cl-; mmol/L)
  - Gamma-GT (IU/L)
  - Aspartate aminotransferase (ASAT; IU/L), serum glutamic oxaloacetic transaminase (SGOT)
  - Alanine aminotransferase (ALAT; IU/L), serum pyruvic oxaloacetic transaminase (SGPT)
  - Alkaline phosphatase, (AP; IU/L)
  - Total protein (g/L)
  - Albumin (g/L)
  - Urea (mmol/L)
  - Glucose (mmol/L)
  - Creatinine (µmol/L)
  - Total bilirubin (µmol/L)
- Total cholesterol (mmol/L)
- Triglycerides (mmol/L)
- Osteocalcin

- C-reactive protein (CRP; mg/L), interleukin-6 (IL-6) and TNFα will be evaluated as efficacy variables (Section 7.3.1.7)

The time points at which different blood volumes are withdrawn for laboratory evaluations are presented in Table 1 below.

Table 1: Time points and blood volumes withdrawn for laboratory evaluations

<table>
<thead>
<tr>
<th>Visit</th>
<th>Blood volume (in mL) withdrawn from each patient during the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 0</td>
<td>Visit 1</td>
</tr>
<tr>
<td>Week</td>
<td></td>
</tr>
<tr>
<td>Safety laboratory (biochemistry and hematology)</td>
<td>10</td>
</tr>
<tr>
<td>ESR</td>
<td>2</td>
</tr>
<tr>
<td>CRP</td>
<td>1</td>
</tr>
<tr>
<td>IL-6 and TNFα</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
</tr>
</tbody>
</table>

It is essential that ICON will be provided with a list of normal laboratory ranges, prior to shipment of study drug. Any change in normal laboratory ranges during the study will additionally be forwarded to ICON. Since all laboratory assessments apart from ESR will be performed by a central laboratory, it is the responsibility of the central laboratory to provide data management (and investigators) with their updated normal ranges.

It is also the responsibility of the central laboratory to provide handling instructions, and to secure identification of the samples by providing respective labels for all probes and shipments. Data from laboratory assessments, particularly of CRP, IL-6 and TNFα from the double-blind treatment phase should not be disclosed to investigators or monitors prior to data base closure (disclosure of the medication code).

7.3.2.3 Hemoccult/guaiac test

Hemoccult/guaiac tests will be performed to assess gastrointestinal safety. The test samples will be developed locally. The investigator will be responsible for evaluating and documenting the test results.
Hemoccult/guaiac tests must be performed prior to randomization at Visit 0 and prior to the end of treatment at Visit 4. In the case of patients experiencing any gastrointestinal AEs, additional Hemoccult/guaiac test must be performed.

The central laboratory will be responsible for providing the Hemoccult/guaiac test kits and detailed handling instructions.

7.3.2.4 Physical examination

The general physical examination prior to the study serves to document the patient’s general state of health and to exclude conditions which may constitute exclusion criteria. Parameters to be documented from general physical examinations are height (which will only be measured at Visit 0) and vital signs (blood pressure and heart rate in the sitting position, and body weight). The following systems will also be assessed as normal or abnormal: eyes, ears, nose, throat, lymph nodes, heart, chest (including breasts), lungs, abdomen, renal, genitalia, anorectal, extremities, musculoskeletal, nervous system, skin, vascular and endocrine (metabolism and nutrition).

7.3.3 Quality-of-life data

Quality of life data includes:

- HAQ-DI, which is also included as efficacy data (Section 7.3.1.5; Appendix I)
- Short Form (SF) 36 (Quality of Life) questionnaire (Appendix I)
- Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) questionnaire (Appendix I)

8. ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

Examples of AEs include one of the following or a combination of two or more of these factors:
● A new sign, symptom, illness, or syndrome
● Abnormal laboratory values, if judged clinically significant in the opinion of the investigator
● Worsening (change in nature, severity or frequency) of a concomitant or pre-existing illness
● An adverse effect of the investigational medicinal product, including comparator or concomitant medication
● Drug interactions
● An adverse effect of an invasive procedure required by the protocol
● An accident or injury

All AEs fall into the categories “non-serious” and “serious”.

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly. Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case the condition should be reported as medical history.

8.1.2 Events not falling under the definition of an adverse event

In this study no medical events have been determined which would not fall under the definition of an adverse event.

8.1.3 Definition of a serious adverse event

A SAE is any untoward medical occurrence that at any dose (including overdose):
● Results in death
● Is life-threatening
  - “Life-threatening” means that the patient was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe
● Requires inpatient hospitalization or prolongation of existing hospitalization
  - This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the AE, or that they occurred as a consequence of the event
  - Visits to a hospital by ambulance without admission will not be regarded as hospitalization unless the event fulfils any other of the serious criteria
Results in persistent or significant disability or incapacity

- “Persistent or significant disability or incapacity” means a permanent or significant and substantial disruption of a person’s ability to carry out normal life functions

Is a congenital anomaly or birth defect

Is an important medical event

- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. 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 should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

- A diagnosis of cancer/ malignant tumor during the course of a treatment should always be considered as medically important

Clarification of the difference in meaning between “severe” and “serious”:

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Other events to be treated as serious adverse events

Misuse and overdose

Drug misuse and drug overdose should be reported in the same format and within the same timelines as a SAE, even if they may not result in an adverse outcome.

Exposure to drug during pregnancy or lactation

In principle, pregnancy and the lactation period are exclusion criteria for clinical studies involving investigational drugs, which are not directly related to the respective conditions. In the event of a pregnancy occurring during the course of this particular study, the subject should be withdrawn from study, but closely followed-up during the entire course of the pregnancy and postpartum period. All recommendations described in the investigational drug brochure during pregnancy and lactation have to be carefully considered.
The Sponsor must be notified without delay. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Off-spring should be followed up for at least 8 weeks after delivery.

Longer observation periods may be determined by the Sponsor if an adverse outcome of the pregnancy was observed.

8.1.4 Investigational product complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to ICON immediately. The same reporting timelines as for SAEs apply.

8.2 PERIOD OF OBSERVATION

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient provides informed consent (at Week -1) until the end of treatment, or until 30 days after the last study drug administration; whichever comes later.

If the investigator detects a SAE in a study patient after the end of the period of observation, and considers the event possibly related to prior study treatment or procedures, he or she should contact the Sponsor to determine how the AE should be documented and reported.

All AEs that occur in the course of a clinical study regardless of the causal relationship must be monitored and followed up until the outcome is known. There must be documented reasonable attempts to get this information.

It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

8.3 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

8.3.1 Documentation and reporting of adverse events by investigator

The investigator must document all AEs that occur during the observation period set in this protocol (see Section 8.2) on the pages provided in the CRF in accordance with the instructions for the completion of AE reports in clinical studies. These instructions are provided in the investigator file and in the CRF itself.

The following approach will be taken for documentation:

- All AEs (whether serious or non-serious,) must be documented on the “Adverse Event” page of the CRF
- If the AE is serious (see Section 8.1.3), the investigator must complete, in addition to the “AE” page in the CRF, a “SAE Report” form at the time the SAE is detected. This form
must be sent immediately, i.e. within 24 hours upon becoming knowledgeable of the SAE to the safety contact of ICON (see Emergency Contacts on page 4)

- When an “overdose” or “drug misuse” of the investigational product occurs without an AE or if a pregnancy is detected without an adverse outcome, the investigator should only complete a “SAE Report” form and send it to ICON’s safety contact. It should be clearly stated that no AE was observed. In this case, there is no need to complete the “AE” page in the CRF.

Every attempt should be made to describe all AEs in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms should not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

The initial report should be as complete as possible, including details of the current illness and (serious) AE, the reason why the event was considered serious, date of onset and stop date (if applicable), diagnostic procedures and treatment of the event, relevant medical history and concomitant medication and action taken with study medication.

The investigator will also provide an assessment of the severity of the event and causal relationship between the event and the investigational product(s) or study procedures.

The basis of assessing severity and causality is described as:

**Severity**

- **Mild**: Causing no limitation of usual activities; the subject may experience slight discomfort
- **Moderate**: Causing some limitation of usual activities; the subject may experience annoying discomfort
- **Severe**: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain

**Causality assessment**:

The investigator should use medical judgment to determine whether there is a reasonable causal relationship, including all relevant factors such as temporal course and latency, results from de-challenge or re-challenge, pattern of the reaction, known pharmacological properties of the product, and alternative explanations (e.g. other drugs, medical history, concomitant diseases). The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship. Assessment will be documented on the AE and SAE form:

- **Yes**: There is a reasonable causal relationship between the investigational medicinal product and the AE
– **No**: There is no reasonable causal relationship between the investigational medicinal product and the AE

Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a “SAE” form, with the box “Follow-up” checked under “Report type”.

All patients who have AEs, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist’s report should be supplied, if possible.

The Sponsor will identify missing information for each SAE report. Requests for follow up will be sent to ICON for further processing. ICON will require follow up information at regular intervals from the investigators until all queries are resolved or no further information can be reasonably expected. All responses to queries and supply of additional information by the investigator should follow the same reporting route and timelines as the initial report.

8.3.2 Reporting of expeditable adverse events to competent authorities and concerned ethics committee

The Sponsor will report all serious and unexpected AEs, which are judged by either the investigator or the Sponsor as having a reasonable suspected causal relationship (suspected unexpected serious adverse reaction [SUSAR]), to the competent authorities and the concerned EC according to applicable law. Treatment codes will be broken prior to submission to authorities and concerned ECs, by the Sponsor’s safety group, which is an independent entity within the Sponsor. The study team will be kept blinded regarding treatment assignment.

The Sponsor will also inform all investigators in a blinded fashion. Reporting obligations to the local EC of the investigator will be fulfilled by the investigator.

The Sponsor will prepare and submit annual safety reports to competent authorities and concerned ECs.

9. EMERGENCY PROCEDURES

9.1 EMERGENCY CONTACT

In case of a SAE, the investigator must contact the contract research organization (CRO) within one working day by fax at the number provided on page 4 of the protocol. SAEs will be reported as described in Section 8.3.
In case of any protocol or medical issues not related to a SAE the investigator may contact the Sponsor at the numbers provided on page 4 of the protocol.

Patients will receive a patient card with emergency contact numbers.

9.2 EMERGENCY IDENTIFICATION OF INVESTIGATIONAL PRODUCTS

The Sponsor should be contacted before the blind is broken. If it is medically imperative to know what investigational product the patient is receiving, the investigator or authorized person should open the emergency envelope. The investigator or the person who breaks the blind must record the date and the reasons for doing so in the CRF, in the patient’s medical record, and on the emergency envelope. In such cases, treatment with the investigational product must be stopped and the Sponsor must be contacted immediately to determine whether the patient should be withdrawn from the study.

9.3 EMERGENCY TREATMENT

During and after a patient’s participation in the trial, the investigator or institution should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the trial. The investigator or institution should inform a patient when medical care is needed for concurrent illness(es) of which the investigator becomes aware.

10. STATISTICAL CONSIDERATIONS

10.1 ANALYSIS VARIABLES

10.1.1 Demographic and background variables

- Demography: gender, age, race and ethnic origin
- Medical and disease history: duration of RA, age at onset of RA, previous and concomitant illnesses
- Previous and concomitant medication as coded by WHO Drug Reference List. Medication taken for RA will be classed into DMARDs, corticosteroids, NSAIDs, and analgesics
- Study medication: Treatment duration and compliance
10.1.2 Efficacy variables

Primary efficacy variable

The primary efficacy variable will be the ACR20 responder rate after 12 weeks of double-blind treatment with the study medication. Responders will be defined as those whose improvement from baseline to endpoint (12 weeks) fulfill all three of the following criteria:

- ≥20% reduction in the tender joint count (0–28)
- ≥20% reduction in the swollen joint count (0–28)
- ≥20% reduction in 3 of 5 of the following additional measures:
  - Patient assessment of pain (VAS)
  - Patient’s global assessment of disease activity (VAS)
  - Physician’s global assessment of disease activity (VAS)
  - HAQ-DI
  - CRP or ESR as acute-phase reactant. CRP will be used if the CRP value at baseline (Visit 1; Week 0) is above the upper limit of normal (ULN); otherwise the ESR value will be used to calculate the ACR20 responder status

Key secondary efficacy variable

The key secondary efficacy variable will be the relative change (%) in the duration of morning stiffness between baseline and endpoint (12 weeks).

Further secondary efficacy variables are listed below:

- Disease Activity Score (DAS28): DAS28 is a score aggregating data of 28 joints, and is calculated using the following formula:

\[
DAS28 = 0.56 \times \sqrt{\text{number of tender joints}} \\
+ 0.28 \times \sqrt{\text{number of swollen joints}} \\
+ 0.70 \times \ln(\text{ESR, 1st hour}) [\text{mm}] \\
+ 0.014 \times \text{patient’s global assessment of disease activity (VAS)} [\text{mm}]
\]

- EULAR response criteria: Additionally, patients will be classified as patients with good, moderate or no response based on their change in DAS28 (van Gestel et al. 1999)

- Absolute reduction of morning stiffness between baseline and endpoint (12 weeks) and between study visits

- Severity of morning stiffness: 100 mm VAS

- Reoccurrence of stiffness during day (while performing routine activities) (yes/no)

- Tender and swollen joint counts: The analysis of tender joint count and swollen joint count is based on a 28 joint assessment. For each patient, only those joints that are
evaluable at baseline and endpoint will be included in the statistical analysis of joint counts

- Patient assessment of the pain intensity: 100 mm VAS
- Physician’s and patient’s global assessments: 100 mm VAS
- HAQ-DI: The maximum score of all items within each of the 8 categories gives the category score for each patient. The functional disability index is the average of all 8 category scores. A detailed description on how the use of aids/devices is incorporated in the calculation of the score will be given in the statistical analysis plan
- Inflammatory parameters: CRP, ESR, TNFα and IL-6
- Occurrence of pain in morning and evening: 100 mm VAS
- Use of additional analgesics: Use of additional analgesics (no/yes) and the number of days during the first 12 weeks of double-blind treatment will be analyzed
- Short Form 36 (Quality of Life; SF-36): The score of each of the 8 different domains of the SF-36 will be analyzed
- FACIT fatigue scale: This questionnaire comprises multiple questions for each of the 4 categories (physical well-being, social/family well-being, emotional well-being, functional well-being). The statistical analysis of the FACIT fatigue scale will be described in the statistical analysis plan

10.1.3 Safety variables

- AEs: as coded by Medical Dictionary for Regulatory Activities (MedDRA). Only treatment emergent AEs (TEAEs) will be included in the frequency tables
- Laboratory variables (including urinalysis)
- Vital signs: systolic and diastolic blood pressure, heart rate, body weight
- Physical examination (normal/abnormal)
10.2 ANALYSIS POPULATIONS

The primary analysis population for efficacy analyses will be the modified intention-to-treat (ITT) population as defined below. In order to assess the treatment effect using different assumptions from those in the ITT analysis, the primary efficacy and key secondary variables will also be analyzed for the per-protocol (PP) population. All safety analysis will be based on the safety population.

**Modified intention-to-treat population.** All patients who were randomized and received at least one dose of study medication. Patients will be analyzed according to the treatment to which they were randomized.

**Per-protocol population.** All patients who were randomized, treated with study medication and did not have a major protocol deviation (to be defined prior to the unblinding of the database).

**Safety population.** All patients who were randomized and received at least one dose of study medication. Patients will be analyzed according to the treatment which they actually received.

10.3 STATISTICAL METHODS

The statistical analysis will be conducted following the principles as specified in ICH Topic E9 (ICH 1998). Complete details of the statistical analyses and methods, including data conventions, will be described in a separate statistical analysis plan which will be finalized before unblinding.

For all variables measured during screening or at the randomization visit, the last available value prior to the first intake of study medication will be considered as the baseline value. The respective endpoint value is the first available value measured within 3 days of last intake of study medication. If there is no endpoint value according to these criteria, the last available value before last intake of study medication is regarded as the endpoint value.

All efficacy and safety variables will be summarized by treatment group using descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum for continuous data and absolute and relative frequencies for categorical data). Data will be summarized for baseline, endpoint and by visit (if applicable).

10.3.1 Baseline comparability of treatment groups

Descriptive statistics will be presented to assess the distribution of the baseline variables across treatment groups. No statistical test for differences between treatment groups will be applied.
10.3.2 Efficacy analysis

Primary Efficacy Analysis

For the primary efficacy variable, the following null hypothesis will be tested:

- $H_0$: no treatment difference between placebo and Lodotra®

  Versus

- $H_1$: there is a treatment difference between placebo and Lodotra®

The primary efficacy analysis of the ACR20 responder status at the 12 week endpoint will be tested using a logistic regression model with treatment and (pooled) sites as factors with a two-sided significance level of $\alpha=0.05$ for the modified ITT population. The algorithm for the pooling of study sites with small numbers of patients will be specified in the statistical analysis plan. Patients who withdraw from the study before the 12 week visit will be considered non-responders according to the ACR20 criteria.

For the evaluation of the robustness of results the primary efficacy analysis will be repeated for the PP population. Odds ratios for the difference between treatments and the associated 95% confidence interval will be presented for each population.

In order to evaluate the consistency of results across the different study sites, the logistic regression analysis will be repeated with a treatment-by-(pooled) site interaction term included in the model.

Secondary Efficacy Analyses

In addition, comparing the groups by the proportion of patients responding according to the ACR20 criteria, the time between baseline and a patient’s first response to the ACR20 criteria will be analyzed using Kaplan-Meier methodology and treatments will be compared using a log-rank test.

Analysis of covariance (ANCOVA) will be performed on the mean absolute changes from baseline to endpoint for the ACR core set measures. For morning stiffness the relative change from baseline to the 12-week endpoint will be analyzed by ANCOVA. The following factors will be included in the ANCOVA model: treatment, (pooled) sites and the baseline value as the covariate.

Mean absolute and relative changes (if applicable) from baseline to the 12-week endpoint will be calculated for all efficacy variables with the exception of ACR response, EULAR response and number of days with additional analgesic intake.

EULAR response will be analyzed using logistic regression with treatment and (pooled) site as factors, similar to the analysis of the primary efficacy variable.
The between treatment group comparison of the proportion of patients using additional analgesics during the double-blind treatment period will be done using a logistic regression model with treatment and (pooled) sites as factors. The number of days with additional analgesic use will be analyzed using descriptive statistics and non-parametric methodology.

10.3.3 Safety analysis

All safety data will be analyzed descriptively by treatment group.

Adverse events: Absolute and relative frequencies of TEAEs will be calculated by system organ class and preferred term for all AEs, possibly related AEs, SAEs, and AEs leading to withdrawal.

Laboratory data for hematology and clinical chemistry will be analyzed for differential patterns of changes between treatment groups.

The frequency of changes with respect to normal ranges between baseline and endpoint will be tabulated. Frequencies of clinically noteworthy values (defined in the statistical analysis plan) occurring during the study will also be given.

Shifts from normal to abnormal between baseline and endpoint will be evaluated for urinalysis.

Changes in vital signs will be examined at each visit and at endpoint. Frequencies of clinically noteworthy values (defined in the statistical analysis plan) occurring during the study will be presented. Shifts from normal to abnormal between baseline and endpoint will be evaluated for the physical examination.

10.3.4 Missing data

Each patient will be defined as a responder or non-responder at the Week 12 visit according to the ACR20 criteria. Patients who withdraw prematurely will be considered non-responders in the primary analysis. It is assumed that final efficacy assessments will be available and complete for all PP patients.

To investigate the effect of missing data on the primary endpoint, the primary analysis will be repeated for those patients who provide complete ACR20 information at Week 12. Patients who have no complete efficacy assessment after first intake of study medication or who are withdrawn at any time due to lack of efficacy will be considered as non-responders. All other patients without final efficacy data will be regarded as missing and excluded from the analysis in this secondary evaluation.

The key secondary variable (the relative change [%] in the duration of morning stiffness) will be analyzed using an LOCF approach.
All other secondary variables will be analyzed using both LOCF imputation and observed data.

10.4 INTERIM ANALYSIS

No interim analysis is planned for this study.

10.5 SAMPLE SIZE JUSTIFICATION

Superiority of an active treatment versus placebo is defined as an ACR20 response rate on active treatment that is at least 20% higher than that on placebo (e.g. 45% vs. 25%, 50% vs. 30%, or 40% vs. 20%).

The sample size calculation is based on the comparison of two proportions using the $\chi^2$ test and a randomization ratio of 1:2 (placebo: Lodotra®).

Based on a review of selected literature and other similar studies, typical placebo response rates range between 20-30% for ACR20. Assuming an ACR20 response rate of 25% in the placebo group, a total of 294 patients (98 placebo, 196 Lodotra®) are necessary to provide 90% power to detect an ACR20 response rate of 45% in the Lodotra® group at a significance level of $\alpha=0.05$.

It is estimated that a minimum of 350 patients will have to be enrolled into the study to randomize 294 patients.

Assuming a SD of 89% for the key secondary efficacy variable (relative change [%] in morning stiffness) based on the SD reported in the previous Lodotra® study, the calculated sample size of 294 patients (98 placebo, 196 Lodotra®) will have 78% power to detect a difference of 30% between placebo and Lodotra® and 89% power to detect a difference of 35%.

11. ETHICAL AND LEGAL ASPECTS

11.1 GOOD CLINICAL PRACTICE

This study is to be conducted according to globally accepted standards of GCP (as defined in the ICH E6 Guideline for GCP), in agreement with the Declaration of Helsinki from 2000 and in keeping with local regulations.
11.2 DELEGATION OF INVESTIGATOR DUTIES

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

11.3 PATIENT INFORMATION AND INFORMED CONSENT

Before being enrolled in the clinical study, patients must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

After reading the Patient Information Leaflet/Informed Consent Form, the patient must give consent in writing on the informed consent form. The patient’s consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

If the patient is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (e.g., the patient’s thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent form.

A copy of the Patient Information Leaflet and the signed consent form must be given to the patient. The original signed and dated consent form will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The investigator should inform the patient’s primary physician about the patient’s participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.

11.4 CONFIDENTIALITY

Patient names will not be supplied to the Sponsor or representatives of the Sponsor. A patient number and patient initials will be recorded in the CRF, and if the patient name appears on any other document (e.g., laboratory report), it must be removed on the copy of the document to be supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.
The patients must be informed that representatives of the Sponsor, CRO, EC, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

11.5 PROTOCOL AMENDMENTS

Neither the investigator nor the Sponsor will alter this clinical study protocol without obtaining the written agreement of the other. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the clinical study protocol.

11.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the clinical study protocol, patient information leaflet and informed consent form, and any other appropriate documents will be submitted to the EC or IRB. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements. As required by local regulation or by the EC or IRB, the Sponsor or investigator will also submit the financial arrangements for the study or other financial interests of the investigator in the investigational drug or Sponsor company to the EC or IRB.

Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

If applicable, the EC or IRB and authorities must be informed of all subsequent amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the patient information leaflet and informed consent form should also be revised.

The investigator must keep a record of all communication with the EC or IRB and, if applicable, between a coordinating investigator and the EC or IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.
11.7 ONGOING INFORMATION FOR ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

Unless otherwise instructed by the EC or IRB or local law, the Sponsor or the investigator must submit to the EC or IRB:

- Information on AEs that are serious AND unexpected AND associated with the investigational product from the investigator’s site, as soon as possible
- Expedited safety reports from the Sponsor, as soon as possible
- Periodic reports on the progress of the study
- Deviations from the protocol

11.8 DISCONTINUATION OF THE STUDY

The study must be discontinued at the site on completion.

The whole study may be discontinued in the event of any of the following:

- Inefficacy of the study drug
- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development

Completion or premature termination of the study will be reported by the Sponsor to the regulatory agency and by the Sponsor or investigator to the EC or IRB as required by local regulation or by the EC or IRB.

Furthermore, the Sponsor or the investigator has the right to close the study site at any time. As far as possible, premature discontinuation should occur after mutual consultation.

Study materials must be returned, disposed of or retained as directed by the Sponsor.

11.9 RECORD RETENTION

The investigator must obtain approval in writing from the Sponsor before destruction of any records, and must document any change of ownership.

Study records should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal
discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Patient identification codes have to be retained according to ICH GCP or for at least 15 years after the completion or discontinuation of the trial whatever is the longest period in time.

If an investigator leaves an investigational site, the responsibility for archiving of all study related records has to be transferred to another person (e.g. other investigator). The Sponsor has to be informed about any change in responsibility.

11.10 LIABILITY AND INSURANCE

Liability and insurance provisions for patients and investigators participating in this study are given in separate agreements.

11.11 FINANCIAL DISCLOSURE

Before the start of the study, the investigator will disclose to the Sponsor any proprietary or financial interests he or she might hold in the investigational products or the Sponsor company as outlined in the financial disclosure form provided by the Sponsor. The investigator agrees to update this information in the case of significant changes during the study or within one year of its completion. The investigator also agrees that, where required by law or regulation, the Sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Where required by regulation, the Sponsor will also submit the financial arrangements for the study to the regulatory authorities.

Similar information will be provided by each subinvestigator to whom the investigator delegates significant study related responsibilities.

12. STUDY MONITORING AND AUDITING

Monitoring and auditing procedures developed or endorsed by the Sponsor will be followed in accordance with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

12.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

Monitoring will be done by personal visits from a representative of the Sponsor (clinical monitor) who will check the CRFs for completeness and clarity, and crosscheck them with source documents. Questionnaires completed by patients will be included in the CRF, and
there will be no other source documentation available. In addition to the monitoring visits, frequent communications (letter, telephone, and fax), by the clinical monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

Study close-out will be performed by the clinical monitor upon closure of the study.

12.2  ON-SITE AUDITS

Domestic and foreign regulatory authorities, the EC or IRB, and an auditor authorized by the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that patient names are removed on the copies to ensure confidentiality.

13.  DOCUMENTATION AND USE OF STUDY FINDINGS

13.1  DOCUMENTATION OF STUDY FINDINGS

Only hard-copy CRFs will be used.

A CRF will be provided for each patient.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the CRF. Details of CRF completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the CRF, the names, positions, signatures, and initials of these persons must be supplied to the Sponsor.

The investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

A source data location list will be prepared before study start. This list will be filed in both the trial master file and the investigator study file and updated as necessary.

The completed CRF must be reviewed and signed by the investigator named in the clinical study protocol or by a designated subinvestigator.

The Sponsor will retain the originals of all CRFs. The investigator will retain a copy of all completed CRF pages.
13.2 USE OF STUDY FINDINGS

All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

The Sponsor has full ownership of the original CRFs completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator’s name, address, qualifications, and extent of involvement.

The Sponsor will ensure that a final report on the study is prepared.

As required by local regulation or by the EC or IRB, a summary of the clinical study will be submitted by the Sponsor to the regulatory authorities and by the Sponsor or investigator to the EC or IRB.

All materials, documents and information supplied by the Sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the Sponsor.

13.3 PUBLICATIONS

Nitec Pharma is dedicated to support free exchange of relevant scientific information. By signing the final protocol, the principal investigator agrees to keep all information and results concerning the study and the investigational product confidential as long as the data remain unpublished. The Sponsor or CRO will document the results of the clinical trial in a study report. Prior to any submission, all manuscripts/abstracts must be presented to the Sponsor for possible comments.

If requested, the investigator will withhold publication to allow for filing a patent application or taking such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.
14. DECLARATIONS OF SPONSOR AND INVESTIGATORS

14.1 SPONSORS APPROVAL OF STUDY PROTOCOL

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Stephan Witte, PhD
Chief Medical Officer

Achim Schäffler, PhD
EVP R&D and Technical operations

21 JAN 2008
Date
14.2 DECLARATION OF COORDINATING INVESTIGATOR

I hereby agree that I will assume the responsibilities of the Coordinating Investigator in this study, including reviewing and signing the following: study protocol, amendments to the protocol if applicable, and final study report.

Prof. Dr. Frank Buttgereit

Date 22 Jan 2008
14.3 DECLARATION OF INVESTIGATOR

I agree to conduct this study in accordance with the requirements of this Clinical Study Protocol and also in accordance with the following:

- The principles of the “Declaration of Helsinki” (as amended in Tokyo, Venice, Hong Kong and South Africa)
- Good Clinical Practice Respective local laws and regulations

Signature of responsible study personnel at site

_________________________________________  ___________
Investigator                               Date
15. REFERENCES


16. APPENDICES

APPENDIX I: QUESTIONNAIRES AND SCORES

- Short Form (SF)-36

Your Health and Well-Being

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

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

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

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□₁</td>
<td>□₂</td>
<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
</tbody>
</table>
2. **Compared to one year ago, how would you rate your health in general now?**

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Yes, limited</th>
<th>Yes, limited</th>
<th>No, not limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>a lot</td>
<td>a little</td>
<td>at all</td>
</tr>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports ........................................... □ ................ □ : ............. □ :
- **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf ........................................... □ ................ □ : ............. □ :
- Lifting or carrying groceries ........................................... □ ................ □ : ............. □ :
- Climbing **several** flights of stairs ............................... □ ................ □ : ............. □ :
- Climbing **one** flight of stairs ....................................... □ ................ □ : ............. □ :
- Bending, kneeling, or stooping ........................................... □ ................ □ : ............. □ :
Walking more than a mile .................................. □ □ □
Walking several hundred yards ...................... □ □ □
Walking one hundred yards ............................ □ □ □
Batting or dressing yourself ............................ □ □ □

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

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. Cut down on the amount of time you spent on work or other activities

b. Accomplished less than you would like

c. Were limited in the kind of work or other activities

d. Had difficulty performing the work or other activities (for example, it took extra effort)
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Cut down on the amount of time you spent on work or other activities
  - □ □ □ □ □

- Accomplished less than you would like
  - □ □ □ □ □

- Did work or other activities less carefully
  - □ □ □ □ □

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

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
<td>□ □ □ □ □</td>
</tr>
</tbody>
</table>
7. **How much bodily pain have you had during the past 4 weeks?**

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

a. Have you been very nervous? □ 1 □ 2 □ 3 □ 4 □ 5

b. Have you felt so down in the dumps that nothing could cheer you up? □ 1 □ 2 □ 3 □ 4 □ 5

c. Have you felt calm and peaceful? □ 1 □ 2 □ 3 □ 4 □ 5

d. Did you have a lot of energy? □ 1 □ 2 □ 3 □ 4 □ 5

e. Have you felt downhearted and depressed? □ 1 □ 2 □ 3 □ 4 □ 5

f. Did you feel worn out? □ 1 □ 2 □ 3 □ 4 □ 5

g. Have you been happy? □ 1 □ 2 □ 3 □ 4 □ 5

h. Did you feel tired? □ 1 □ 2 □ 3 □ 4 □ 5

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

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

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

THANK YOU FOR COMPLETING THESE QUESTIONS!
- Functional Disability Index of the Health Assessment Questionnaire (HAQ-D1)

**HEALTH ASSESSMENT QUESTIONNAIRE**

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.

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

<table>
<thead>
<tr>
<th>DRESSING &amp; GROOMING</th>
<th>Without ANY Difficulty</th>
<th>With SOME Difficulty</th>
<th>With MUCH Difficulty</th>
<th>UNABLE To Do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Dress yourself, including tying shoelaces and doing up buttons?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>- Wash your hair?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RISING</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stand up from a straight chair?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>- Get in and out of bed?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EATING</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cut up your meat?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>- Lift a full cup or glass to your mouth?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>- Open a new milk carton?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WALKING</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Walk outdoors on flat ground?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>- Climb up five steps?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>
Please tick any of the following AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:

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

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

_____ Dressing and Grooming  
_____ Eating
_____ Rising  
_____ Walking

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

<table>
<thead>
<tr>
<th>HYGIENE</th>
<th>Without ANY Difficulty</th>
<th>With SOME Difficulty</th>
<th>With MUCH Difficulty</th>
<th>UNABLE To Do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Wash and dry your body?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>- Have a bath?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
<tr>
<td>- Get on and off the toilet?</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>

| 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? | _____ | _____ | _____ | _____ |
GRIP

Are you able to:

- Open car doors? ______ ______ ______ ______
- Open jars which have been previously opened? ______ ______ ______ ______
- Turn taps on and off? ______ ______ ______ ______

ACTIVITIES

Are you able to:

- Go shopping? ______ ______ ______ ______
- Get in and out of a car? ______ ______ ______ ______
- Do chores such as vacuuming or gardening? ______ ______ ______ ______

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

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

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

- Hygiene ______
- Gripping and opening things ______
- Reaching ______
- Shopping and housework ______

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?:

PLACE A VERTICAL (L) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN ________________________________________________ SEVERE PAIN
0 100
**Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)**

**FACIT-F (Version 4)**

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy.........................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have nausea ..........................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my physical condition, I have trouble meeting the needs of my family........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have pain ............................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by side effects of treatment.....</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel ill ...............................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am forced to spend time in bed ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at all</td>
<td>A little bit</td>
<td>Somewhat</td>
<td>Quite a bit</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>------------</td>
<td>--------------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>GS1</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>GS2</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>GS3</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>GS4</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>GS5</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>GS6</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS7</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>EMOTIONAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some-what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel sad ...........................................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with how I am coping with my illness ...........................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am losing hope in the fight against my illness ...............................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel nervous ....................................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about dying ..............................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that my condition will get worse ................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>FUNCTIONAL WELL-BEING</td>
<td>Not at all</td>
<td>A little bit</td>
<td>Somewhat</td>
<td>Quite a bit</td>
<td>Very much</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>----------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>I am able to work (include work at home) ...........................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My work (include work at home) is fulfilling .....................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to enjoy life ..............................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have accepted my illness ..........................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am sleeping well ....................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am enjoying the things I usually do for fun ....................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am content with the quality of my life right now ..................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>ADDITIONAL CONCERNS</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel fatigued ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel weak all over ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel listless (“washed out”) ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel tired ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble starting things because I am tired ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble finishing things because I am tired ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have energy ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to do my usual activities ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I need to sleep during the day ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am too tired to eat ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An</td>
<td>I need help doing my usual activities ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>I am frustrated by being too tired to do the things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>I want to do........................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>I have to limit my social activity because I am tired...............................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
• Questionnaire forming part of the Disease Activity Score (DAS)

Rheumatoid Arthritis Activity: Visual Analogue Scale Measurements

Date of VAS Assessments: [Day] [Month] [Year] 2008

Subject’s Pain Assessment for Rheumatoid Arthritis

Please indicate your experience of pain, by marking a single vertical line across the pain scale.

0 | 100
No pain at all | Very intensive pain

Subject’s Global Assessment of Disease Activity

Please indicate your experience of activity, by marking a single vertical line across the activity scale.

0 | 100
Not active at all | Extremely active
Rheumatoid Arthritis Activity: Visual Analogue Scale Measurements (continued)

Date of Physician’s VAS Assessments:

<table>
<thead>
<tr>
<th>Day</th>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>200</td>
</tr>
</tbody>
</table>

Physician’s Global Assessment of Disease Activity

Please indicate your assessment of disease activity, by marking a single vertical line across the activity scale.

0       100
Not active Extremely active

Physician’s Global Assessment of Disease Activity Measurement

(Using a ruler, measure in centimeters to one decimal place from the left hand side of the 100mm scale to the mark made by the subject.)
APPENDIX II: 28 JOINT GRAPH

**DAS 28**

Please highlight the tender and swollen joints in the chart below and enter the exact number in the respective boxes in the CRF.

Tender joints  
Swollen joints