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EXTENDED REPORT

Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2)

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ABSTRACT

Objective To assess the efficacy and safety of low-dose prednisone chronotherapy using a new modified-release (MR) formulation for the treatment of rheumatoid arthritis (RA).

Methods In this 12-week, double-blind, placebo-controlled study, patients with active RA (n=350) were randomised 2:1 to receive MR prednisone 5 mg or placebo once daily in the evening in addition to their existing RA disease-modifying antirheumatic drug (DMARD) treatment. The primary end point was the percentage of patients achieving a 20% improvement in RA signs and symptoms according to American College of Rheumatology criteria (ie, an ACR20 response) at week 12. Changes in morning pain, duration of morning stiffness, 28-joint Disease Activity Score and health-related quality of life were also assessed.

Results MR prednisone plus DMARD treatment produced higher response rates for ACR20 (48% vs 29%, p<0.001) and ACR50 (22% vs 10%, p<0.006) and a greater median relative reduction from baseline in morning stiffness (55% vs 35%, p<0.002) at week 12 than placebo plus DMARD treatment. Significantly greater reductions in severity of RA (Disease Activity Score 28) (p<0.001) and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue score) (p=0.003) as well as a greater improvement in physical function (36-item Short-Form Health Survey score) (p<0.001) were seen at week 12 for MR prednisone versus placebo. The incidence of adverse events was similar for MR prednisone (43%) and placebo (49%).

Conclusion Low-dose MR prednisone added to existing DMARD treatment produced rapid and relevant improvements in RA signs and symptoms.

ClinicalTrials.gov, number NCT00650078

INTRODUCTION

Glucocorticoids such as prednisone are established components of treatment strategies for many inflammatory conditions, such as rheumatoid arthritis (RA), and are widely used.[1–3] Accumulating evidence suggests that low-dose treatment is well tolerated and minimises the risk of the undesirable effects associated with higher doses.[4] However, there is still a need to improve the risk–benefit profile for these valuable anti-inflammatory drugs by increasing the efficacy of low-dose treatment. One promising approach is chronotherapy, in which the delivery of treatment is coordinated with circadian biological rhythms. The chronotherapeutic approach has shown promise in several therapeutic areas, including the management of hypertension, allergic rhinitis and bronchial asthma.[5–7]

Chronotherapy may be particularly appropriate for RA because symptoms follow circadian rhythms, with impaired function due to pain and joint stiffness commonly being most severe in the early morning.[8 9] Emergence of these symptoms follows the increase in serum levels of interleukin 6 (IL-6; a key inflammatory mediator), tumour necrosis factor α (TNFα) and other proinflammatory cytokines that occur late at night.[9–13] Nocturnal secretion of cortisol, which can counter the effects of increased IL-6 levels, is also perturbed in patients with RA and may contribute to the emergence of morning symptoms.[8 14] These observations suggest that the optimal time for delivery of glucocorticoid treatment is during the night, to mimic the normal circadian rhythm of cortisol secretion and target the effects of nocturnal proinflammatory stimuli.

A modified-release (MR) formulation of prednisone has been developed to deliver prednisone chronotherapy. This innovative tablet uses a programmed-release mechanism to release prednisone approximately 4 h after ingestion (ie, at approximately 02:00 am if the patient takes the tablet at 10:00 pm). We report the results of a double-blind, placebo-controlled, multicentre study (Circadian Administration of Prednisone in Rheumatoid Arthritis, CAPRA-2) that investigated the efficacy and safety of low-dose prednisone chronotherapy in patients with active RA.

This is the first rigorous placebo-controlled study to investigate the efficacy of low-dose prednisone in patients with active disease receiving disease-modifying antirheumatic drug (DMARD) treatment and according to current standards. It thus allows comparison with the results of recent studies of other treatments in patients with active RA.

METHODS

Study design

In this 12-week, double-blind, parallel-group, placebo-controlled study, following a 1-week screening period, eligible patients were randomised 2:1 to receive MR prednisone (5 mg) or placebo once daily, taken with or after their evening meal, in addition to their standard RA treatment.

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the ethics committees and institutional review boards of all centres, and all patients provided written informed consent before study-related procedures. The trial is registered at ClinicalTrials.gov, number NCT00650078.

Patients

Patients aged 18–80 years with a diagnosis and documented history of RA and who had been taking DMARDs for at least 6 months were eligible for inclusion. Patients were also required to have had a duration of morning stiffness of at least 45 min on at least 4 days within the 7 days of screening, a swollen joint count of ≥4 and a tender joint count of ≥4. Patients receiving oral glucocorticoids within 6 weeks of the screening visit were excluded from the study (see online supplementary material for further details). The study protocol prohibited initiation of any new DMARD or non-steroidal anti-inflammatory drug (NSAID) treatment during the study; changes to existing DMARD treatment (dosing and frequency) were also prohibited.

Outcomes and follow-up

Scheduled study visits occurred at baseline and weeks 2, 6 and 12, and were to occur between 08:00 and 10:00 pm. At each visit, doctors assessed the number of tender and swollen joints and global disease activity, and patients assessed pain and global disease activity and completed the Functional Disability Index of the Health Assessment Questionnaire.[15] Disease activity at each visit was determined using the 28-joint Disease Activity Score (DAS28).[16] Assessments of pain and global disease activity were made using 0–100 mm visual analogue scales (0=no pain/not active at all; 100=very intense pain/extremely active). Blood samples were collected at each study visit.

Throughout the study, patients completed a diary card twice daily. In the mornings they recorded whether they had joint stiffness and its severity, the time of resolution of joint stiffness and pain levels on waking. Evening assessments included pain intensity during the day and whether the patient had experienced recurrence of stiffness. Patients assessed their health status using the 36-item Short-Form Health Survey (SF-36),[17 18] and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire[19 20] at baseline and week 12. Safety assessments (recording of adverse events (AEs) and vital signs) were performed at each study visit according to standard procedure (ie, without using checklists with predefined events).

The primary efficacy end point was the proportion of patients with a 20% improvement in RA signs and symptoms according to American College of Rheumatology (ACR) criteria (ie, an ACR20 response)[21] at week 12. A key secondary end point was the change in duration of morning stiffness between baseline and week 12. (See online supplementary material for details of secondary end points.)

Statistical analysis

The study aimed to demonstrate a difference of at least 20% in ACR20 for MR prednisone versus placebo at week 12. The sample size calculation was based on comparison of two proportions using the χ^2 test and a randomisation ratio of 2:1 for MR prednisone:placebo. Assuming an ACR20 response rate of 25% for placebo, 294 patients would be required to provide 90% power to detect an ACR20 response rate of 45% in the MR prednisone group at a significance level of α=0.05. The study therefore aimed to randomise at least 294 patients; in order to account for potential drop-outs, a total of 350 patients were recruited to the study.

Duration of morning stiffness was the difference between the time of resolution of morning stiffness and the time of waking. The difference between the treatment groups was assessed using the median and the 95% CI of the median, computed using the Hodges–Lehmann method. (See supplementary material for further details.)

RESULTS

Study population

A total of 350 patients were randomised between April 2008 and February 2009; of these, 323 (92.3%) completed the study (figure 1 and supplementary table 1). The main reasons for early withdrawal were AEs and patient requests. Demographics and baseline disease characteristics were generally well balanced between the two treatment groups (table 1). The study population was primarily female (84%), aged >45 to <65 years (70%), and about half of the study population (55%) had had RA for at least 5 years. All patients had previously received treatment for RA: 99% with DMARDs and 73% with NSAIDs.

Virtually all patients (>98%) received concomitant DMARD treatment, the most frequently used being methotrexate (73.7% of patients), sulfasalazine (14.6%) and leflunomide (11.1%). Analgesic use was similar between treatment groups (MR prednisone, 83.1%; placebo, 86.6%). The most frequently used analgesics were anilides (27.4% of patients), acetic acid derivatives (25.1%) and propionic acid derivatives (17.1%). Detailed analysis showed no significant changes in DMARD and NSAID use between baseline and end of study (supplementary table 2) indicating that observed results were not confounded by changes in concomitant treatment.

Efficacy

ACR response rate

ACR20 and ACR50 response rates at week 12 were significantly greater with MR prednisone than with placebo. At week 12, 48% of patients receiving MR prednisone achieved an ACR20 response, compared with 29% in the placebo group, a difference of 19% (p<0.001). The response was achieved rapidly: a significant difference in ACR20 response rate between treatment groups was evident at week 2, and the difference remained significant throughout the study (p<0.005) (figure 2A).

ACR50 responder rates were numerically greater with MR prednisone than with placebo at all time points, and the difference was significant at weeks 6 and 12 (22% vs 10% at week 12, p<0.006). Few patients had an ACR70 response at week 12: 7% of those taking MR prednisone and 3% of placebo recipients (p=0.10).

Individual ACR core set measures

All individual ACR core set measures except C-reactive protein and erythrocyte sedimentation rate showed significantly greater improvements from baseline to week 12 with MR prednisone than with placebo (table 2). Changes from baseline were also significantly different between the placebo and MR prednisone groups at weeks 2 and 6 for all clinical end points (p<0.05).

Patients achieving low disease activity

MR prednisone significantly increased the proportion of patients achieving low disease activity (defined as having a 28-joint Disease Activity Score (DAS28)≤3.2) after 6 weeks (p<0.001) and 12 weeks (p=0.0109) of treatment (supplementary table 3).

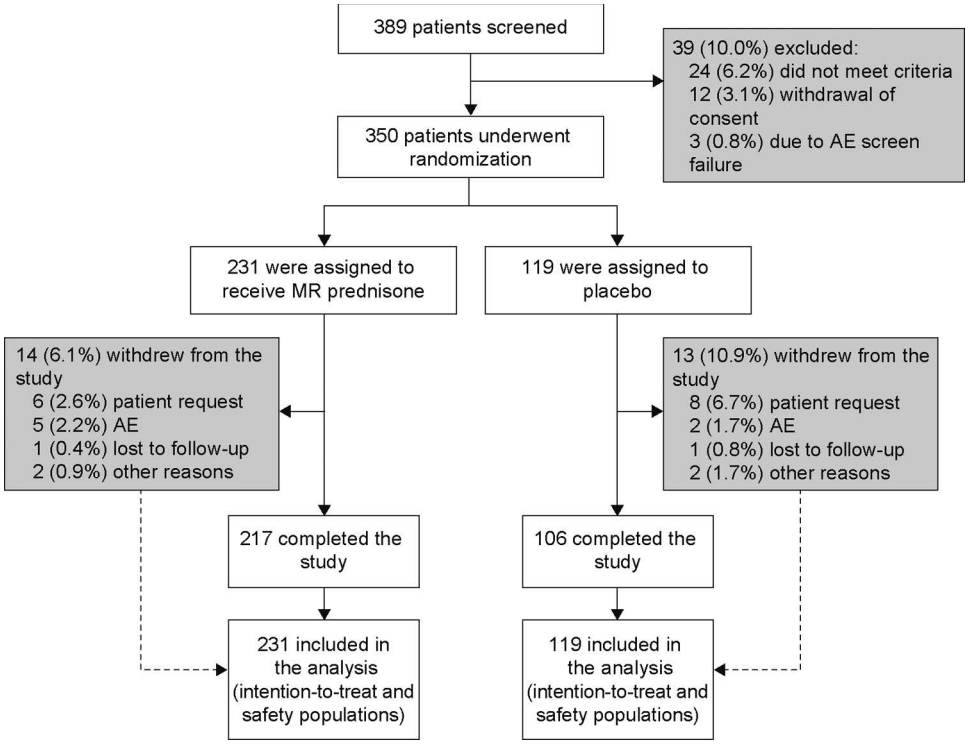

Figure 1 Patient disposition. A total of 350 patients were enrolled from 50 centres in six countries: Germany (3 centres, 3 patients), UK (3 centres, 12 patients), Poland (10 centres, 145 patients), Hungary (9 centres, 102 patients), Canada (2 centres, 13 patients) and USA (23 centres, 75 patients). AE, adverse event; MR, modified release.

At 12 weeks, 11.3% patients in the MR prednisone group had achieved a DAS28 score <2.6 (disease remission or, according to Felson *et al*,[22] minimal disease activity) compared with 6.7% in the placebo group.

Morning stiffness

At baseline, the median duration of morning stiffness was similar between the two treatment groups: MR prednisone, 127 min; placebo, 139 min. At week 12, the median duration of morning stiffness was 46 min in the MR prednisone group (median relative reduction from baseline of 55%), compared with 79 min for placebo (median relative reduction from baseline of 35%). The difference between groups in median relative reduction in duration of morning stiffness was significant at weeks 2, 6 and 12 ($p<0.004$ for all comparisons) (figure 2B). Significantly greater decreases in the severity of morning stiffness and recurrence of stiffness later in the day were also seen for MR prednisone compared with placebo ($p\leq0.01$) (table 2). Further analysis showed no correlation between disease duration and effect on morning stiffness (supplementary table 4) and a regression analysis showed that duration of RA was not a predictor of reduced duration of morning stiffness ($p=0.8433$).

Morning and evening pain

At baseline, both groups reported having considerable morning pain (table 1). Reductions in morning pain from baseline were seen in both treatment groups and were significantly greater in the MR prednisone group at all time points ($p\leq0.05$) (table 2). Significantly greater reductions in evening pain from baseline were also seen for the MR prednisone group ($p<0.05$) (table 2).

Health-related quality of life

At baseline, patients were experiencing considerable fatigue compared with the general population, as indicated by mean FACIT-F scores (MR prednisone, 29; placebo, 29; general population, 44).[19] FACIT-F scores increased in both treatment groups over the course of the study, indicating a reduction in fatigue; the change was significantly greater in the MR prednisone group ($p=0.003$) (table 2).

Improvements in physical function and mental function were also observed over the course of the study in both treatment groups, according to SF-36 assessments (table 2). At baseline, mean scores for physical function (MR prednisone, 32; placebo, 31) were well below that of the US general population—namely, 50.[18] The improvement in physical function was significantly greater in the MR prednisone group (3.6 vs 1.3, $p<0.001$).

Laboratory variables

IL-6 levels at screening were highly variable (table 1), and more than 50% of patients had levels below the limit of detection. Over the 12-week study, IL-6 levels decreased in both treatment groups. The decrease in IL-6 was greater in the MR prednisone group as evident from the geometric mean titre ratio of 0.8 (95% CI 0.7 to 0.9). Minor increases in C-reactive protein levels and decreases in erythrocyte sedimentation rate were seen over the course of the study and were similar in the two treatment groups (table 2). TNFα levels in the two groups were comparable at baseline (table 1) and levels remained unchanged over the 12-week study; the geometric mean titre ratio was 1.0 (95% CI 0.97 to 1.04) for the change in TNFα levels between treatments.

Safety and tolerability

MR prednisone was generally well tolerated, and there were no deaths or life-threatening AEs. The incidence of AEs was slightly lower in the MR prednisone group than the placebo group (43% vs 49%). The incidence of AEs regarded by investigators as

Table 1 Demographics and baseline disease characteristics

Characteristics	MR prednisone (n=231)	Placebo (n=119)
Demographic and disease characteristics		
Age, years		
Mean±SD	57.1±9.9	57.5±9.6
Median (range)	57.0 (27–80)	58.0 (32–76)
Female sex, n (%)	192 (83.1)	102 (85.7)
White race, n (%)	226 (97.8)	118 (99.2)
BMI, mean±SD, kg/m^2	28.0±5.8	28.1±5.5
Duration of RA		
Mean (years)	7.98	7.94
<2 Years, n (%)	41 (17.7)	29 (24.4)
Previous RA treatments, n (%)		
DMARDs	228 (98.7)*	119 (100)
NSAIDs	166 (71.9)	88 (73.9)
Other analgesics	84 (36.4)	53 (44.5)
Biological treatments	1 (0.4)	1 (0.8)
ACR core set measures, mean±SD (unless stated)		
Tender joint count	12.6±6.17	12.5±5.94
Swollen joint count	8.4±4.40	8.6±4.65
Patient assessment of pain†‡	58 (3–96)	51 (0–95)
Patient assessment of disease activity†	57.4±20.1	50.9±20.9
Physician assessment of disease activity†	55.2±16.1	54.1±17.4
HAQ-DI score	1.3±0.6	1.3±0.6
CRP, mg/l‡	5.2 (<0.05–91.5)	5.3 (0.1–136.5)
ESR, mm/h‡	32 (4–104)	30 (2–115)
Other clinical end points, mean±SD		
Duration of morning stiffness, min	152.0±92.4	156.7±87.7
Severity of morning stiffness†	54.6±21.7	50.7±21.3
Recurrence of stiffness, % of days	68.3±39.0	72.1±37.3
Morning pain score†	54.9±21.6	50.5±22.4
Evening pain score†	49.9±23.5	47.8±21.9
DAS28	5.2±0.8	5.1±0.8
Health-related quality of life, mean±SD		
FACIT-F score	28.8±10.4	28.7±10.7
SF-36 physical components summary score	31.6±7.0§	31.5±6.9
SF-36 mental components summary score	45.3±10.7§	45.4±9.6
Inflammatory markers, median (range)		
IL-6, pg/ml	<5 (<5–3215)¶	<5 (<5–266)
TNFα, pg/ml	<5 (<5–65)¶	<5 (<5–15)

*Three patients in the MR prednisone group did not take DMARDs during the study, but they were not uncovered until unblinding.
†Values in mm, measured using a 0–100 visual analogue scale.
‡Data presented as median (range).
§Data missing for two patients.
¶Data missing for one patient.
BMI, body mass index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Functional Disability Index of the Health Assessment Questionnaire; IL-6, interleukin 6; MR, modified release; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SF-36, 36-item Short-Form Health Survey; TNF, tumour necrosis factor.

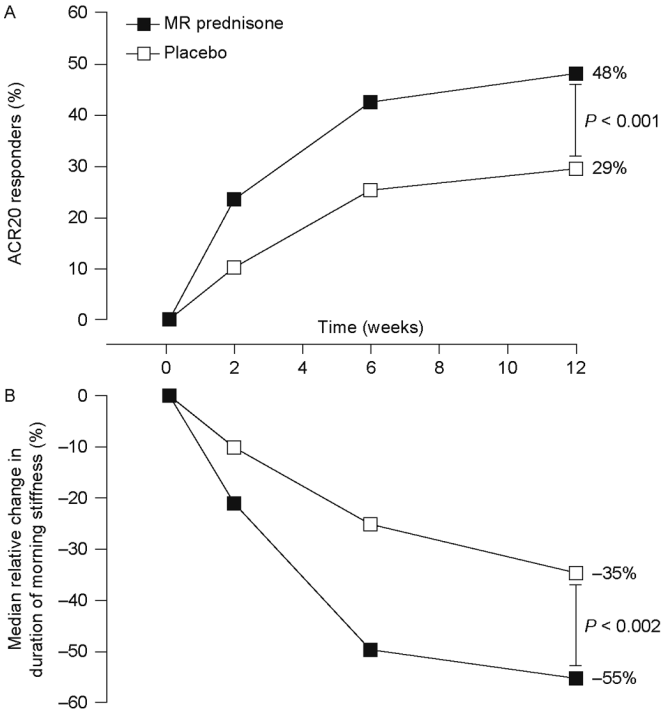

Figure 2 Improvements in rheumatoid arthritis symptoms. (A) Percentage of patients achieving a 20% improvement in rheumatoid arthritis signs and symptoms according to American College of Rheumatology criteria (ACR20) (primary end point). p<0.003 for the between-group difference at weeks 2, 6 and 12. (n Values for weeks 2, 6 and 12 were 231, 229 and 229, respectively, for the modified-release (MR) prednisone group and 119, 119 and 119, respectively, for the placebo group.) (B) Change in duration of morning stiffness from baseline. p<0.004 for the between-group difference at weeks 2, 6 and 12. (n Values for weeks 2, 6 and 12 were 228, 220 and 216, respectively, for the MR prednisone group and 119, 112 and 107 for the placebo group.)

being related to treatment was similar in the two groups (7.8% vs 8.4%) (table 3). In both treatment groups, the most frequently occurring AEs were related to worsening of the underlying disease—namely, arthralgia and aggravated RA/RA flare-up, and these occurred more frequently in the placebo group. The difference in incidence was statistically significant for arthralgia (p=0.0141), but not for aggravated RA/RA flare-up (p=0.3917). The incidence of infections was similar for the two groups (MR prednisone, 13%; placebo, 12%), as was the incidence of the most frequently reported infection, nasopharyngitis; bronchitis was reported more frequently for the placebo group, though the increase was not significant (table 3). Most events were mild or moderately severe.

Serious AEs were reported for one patient (0.4%) receiving MR prednisone and two (1.7%) receiving placebo (table 3); none of the serious AEs were considered severe or related to study treatment. Six patients withdrew from the study because of AEs, five (2.2%) in the MR prednisone group (due in one case each to: headache, headache and hypertension, glaucoma, RA flare and vomiting) and one (0.8%) in the placebo group (due to headache); all events except the case of RA flare in the MR prednisone group were considered related to treatment. No clinically relevant changes in haematological or biochemical parameters or vital signs were seen during the study.

DISCUSSION

Low-dose MR prednisone chronotherapy has an important clinical effect on symptoms of RA in patients with active disease receiving conventional DMARDs, as evident from ACR20 and ACR50 response rates at week 12 in this study. Clinical responses were achieved rapidly, with most clinical end points showing statistically significant differences for MR prednisone over placebo as early as 2 weeks after the start of treatment, and responses were maintained for the duration of the 12-week study. Significant improvements in health-related quality of life (HRQoL) were also seen. The use of analgesics was similar between groups, indicating that the observed improvements could be attributed to MR prednisone, rather than differences in analgesic medication.

Table 2 Mean change from baseline at week 12 in clinical variables and health-related quality-of-life end points*†

	LSM Change from baseline			
	MR Prednisone	Placebo	LSM Difference±SE	p Value‡
ACR core set measures				
Tender joint count	−4.7	−2.7	−2.0±0.6	0.001
Swollen joint count	−3.3	−2.2	−1.1±0.4	0.009
Patient pain score‡	−21.0	−12.7	−8.3±2.5	0.001
Patient global score‡	−17.3	−7.9	−9.3±2.5	<0.001
Physician global score‡	−22.8	−13.1	−9.6±2.2	<0.001
HAQ-DI score	−0.238	−0.079	−0.16±0.04	<0.001
CRP, mg/l	0.86	0.88	0.98§	0.86
ESR after 1 h, mm/h	−7.3	−5.9	−1.4±1.5	0.34
Other clinical end points				
Severity of morning stiffness‡	−27.4	−19.6	−7.8±2.8	0.007
Recurrence of stiffness, % of days (mean)	−20.3	−6.7	−13.6±4.5	0.003
Morning pain score‡	−23.1	−16.4	−6.7±2.6	0.012
Evening pain score‡	−20.2	−14.9	−5.3±2.7	0.049
DAS28 score	−1.15	−0.63	−0.52±0.13	<0.001
Health-related quality of life				
FACIT-fatigue score	3.8	1.6	2.2±0.8	0.003
SF-36 physical component score	3.6	1.3	2.3±0.6	<0.001
SF-36 mental component score	2.0	0.9	1.1±0.7	0.14

*Plus-minus values are means±SD.
†See figure 2 for changes in ACR20 response rate and duration of morning stiffness. Changes in interleukin 6 and tumour necrosis factor α from baseline to week 12 are described in the text.
‡Values in mm, measured using a 0–100 visual analogue scale.
§Geometric mean titre ratio for MR prednisone versus placebo.
ACR, American College of Rheumatology; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Functional Disability Index of the Health Assessment Questionnaire; LSM, least-squares mean; MR, modified release; SF-36, 36-item Short-Form Health Survey.

Table 3 Adverse events

Event, n (%)	MR prednisone n=231	Placebo n=119
Any AE	99 (42.9)	58 (48.7)
Treatment-related AE	18 (7.8)	10 (8.4)
AEs leading to discontinuation*	5 (2.2)	1 (0.8)
Severe AEs†	3 (1.3)	5 (4.2)
Serious AEs‡	1 (0.4)	2 (1.7)
AEs reported in >1% of patients		
Arthralgia	24 (10.4)	24 (20.2)
Aggravated RA/RA flare-up	15 (6.5)	11 (9.2)
Nasopharyngitis	11 (4.8)	4 (3.4)
Headache	9 (3.9)	5 (4.2)
Hypertension	5 (2.2)	1 (0.8)
Diarrhoea	4 (1.7)	1 (0.8)
Rash	4 (1.7)	1 (0.8)
Bronchitis	3 (1.3)	5 (4.2)
Back pain	3 (1.3)	1 (0.8)
Vomiting	3 (1.3)	1 (0.8)
Peripheral oedema	2 (0.9)	2 (1.7)
Haematuria	1 (0.4)	3 (2.5)

*AEs leading to discontinuation were headache (n=2), glaucoma (n=1), vomiting (n=1), exacerbation of RA (n=1), anxiety (n=1), and hypertension (n=1) for the MR prednisone group, and headache (n=1) for the placebo group. All AEs except exacerbation of RA were considered to be related to treatment.
†Severe AEs were arthropod bite (n=1), joint sprain (n=1) and arthralgia (n=1) in the MR prednisone group, and arthralgia (three events), aggravated RA/RA flare-up (two events) and one event each of headache, gout and epistaxis in the placebo group.
‡The serious AE in the MR prednisone group was palpitations and chest discomfort. One patient in the placebo group was diagnosed with ischaemic heart disease and another underwent elective uterus extirpation for abnormal cervical cytology. All events were classified as serious because patients required hospitalisation but none was considered related to the study drug.
AE, adverse event; MR, modified release; RA, rheumatoid arthritis.

Prednisone chronotherapy is expected to have a particular impact on morning symptoms of RA. This is borne out in this study, in which MR prednisone reduced the duration of morning stiffness from approximately 2 h at baseline to 46 min at week 12, a median relative reduction of 55% which was approximately 1.5-fold greater than that seen with placebo. Morning pain, severity of morning stiffness and RA severity (according to DAS28 score) were also considerably reduced with MR prednisone over the 12-week study. This is in agreement with results from our previous study (CAPRA-1),[23] in which MR prednisone induced greater improvements in morning stiffness and reductions in IL-6 levels than immediate-release (IR) prednisone. These results suggest that the timing of delivery significantly affects the efficacy of glucocorticoid treatment and that chronotherapy may allow efficacious treatment with lower glucocorticoid doses.

Previous studies of low-dose prednisone have largely investigated the benefits of adding low-dose (≤10 mg/day) IR prednisone to DMARDs in patients with early RA.[25–30] These placebo-controlled studies have demonstrated more rapid improvements in clinical symptoms over the first 6 months of treatment for prednisone compared with placebo, and are thus in agreement with our results obtained in patients with more advanced disease.[25 28–30] While numerical differences in favour of the prednisone group were also evident at 12 or 24 months, differences were no longer statistically significant in most cases.[25–28] However, the addition of low-dose prednisone has been reported to increase the probability of achieving remission over the first year of treatment and of maintaining remission beyond the first year,[30] and to decrease radiographic progression.[25 27–29] Given the similar results reported for IR prednisone and MR prednisone over the first months of treatment, prolonged treatment with MR prednisone can also be expected to slow radiographic progression, but this disease-modifying effect has still to be proved.

We report that MR prednisone was well tolerated. In this 12-week study, the overall incidence of AEs was slightly lower in patients receiving MR prednisone than in those receiving placebo, and none of the serious or severe AEs in the MR prednisone group was considered related to treatment. In addition, there was no evidence for an increased risk of infection with active treatment; indeed the incidence of bronchitis was higher in the placebo group. The incidences of hypertension and discontinuation due to AEs were low but were slightly higher in the MR prednisone group. Notably, the incidences of arthritis and arthralgia reported as AEs were higher in the placebo group, again reflecting the efficacy of MR prednisone. The safety profile of MR prednisone presented here is similar to that seen in the CAPRA-1 study[11 23] and in placebo-controlled studies for IR prednisone.[27 29]

Our study has several limitations. First, patients were required to have morning stiffness of more than 45 min to be included in the study; our results may thus not be directly applicable to patients with less severe disease. Second, this was a 12-week study. This duration is sufficient to demonstrate the initial benefits achieved by adding MR prednisone to DMARD treatment, including improvements in morning function and HRQoL. However, the study did not assess effects on structural damage and disease progression, which would require longer follow-up. Third, while the results of this study demonstrate that short-term treatment with MR prednisone has a similar safety profile

to that of placebo, long-term studies are required to assess the safety and tolerability of prolonged treatment.

In fact, this has already been demonstrated in the open-label extension to the CAPRA-1 study, where patients received either MR prednisone or IR prednisone for 3 months, before receiving MR prednisone for 9 months. The only AEs reported in >2% of patients during the 9-month extension (months 4–12) were RA-related symptoms (14.5%), upper respiratory tract infections (2.8%), back pain (2.8%) and weight increase (2.8%).[11] An integrated safety analysis (supplementary tables 5 and 6) provides further safety data from the full 12 months of CAPRA-1 (either 12 months MR prednisone treatment or 3 months IR prednisone treatment (months 0–3) followed by 9 months MR prednisone treatment (months 4–12) depending on initial randomisation) and combined safety data for patients receiving MR prednisone for 3 months from both CAPRA-1 and CAPRA-2.[31] The incidence of AEs was higher over the 12-month period than for the 3-month period (as would be expected for the longer duration of treatment), though the increase was not proportional to the duration of treatment. For example, the incidence of severe AEs during the first 3 months of treatment was 2.4% (supplementary table 5) compared with 3.3% in patients receiving 12 months MR prednisone treatment (supplementary table 6). Similarly, aggravated RA/RA flare-up was reported in 12.8% of patients during the first 3 months and in 14.2% of patients during the 12-month treatment period (supplementary tables 5 and 6). The only AEs reported in ≥4% of patients receiving MR prednisone for 12 months were aggravated RA/RA flare-up and flushing (supplementary table 6).

In conclusion, the results of this study demonstrate that even at a dose considered to be below substitution levels, MR prednisone chronotherapy is highly effective and well tolerated in patients with RA, providing rapid relief of symptoms and, particularly, improving morning function. Further, longer-term studies are warranted to determine the dose and strategy that optimises the benefit-to-risk ratio for MR prednisone in the management of RA.

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Contributors All authors vouch for the accuracy of data and the analysis, were involved in the decision to publish, and contributed to the interpretation of the data. All authors approved the submitted paper. Medical writing and editorial assistance was provided by Oxford PharmaGenesis. FB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. Study design: The study was designed by Horizon Pharma (SW and UR) in conjunction with FB and other coauthors (MB, RA, KGS). Patient recruitment: FB, DM, JK, JSz, RA, JSu, IIS. Data gathering and analysis: Horizon Pharma (Mannheim, Germany). Statistical analysis: Patricia Rice (CliniRx USA, Inc), Sandrine Cayez (ICON Clinical Research SARL).

Funding Horizon Pharma (formerly Nitec Pharma), Mannheim, Germany and Northbrook, Illinois, USA.

Competing interests FB received consultancy fees, honoraria and travel expenses from Merck Serono, Horizon Pharma (formerly Nitec Pharma) Mundipharma Int Ltd and grant support from Merck Serono and Horizon Pharma. JK received honoraria, consultancy fees, grants and travel expenses paid to his institution from Horizon Pharma (formerly Nitec Pharma), AstraZeneca, CombinatoRx, GlaxoSmithKline, Merck and Wyeth. MB received consultancy fees from Augurex, Bristol-Myers Squibb, CombinatoRx, GlaxoSmithKline, Medimmune, Horizon Pharma (formerly Nitec Pharma), Mundipharma and Roche; honoraria from Genentech, Novartis and Sanofi; and payment for development of educational presentations from Schering-Plough and UCB. REA received consultancy fees and honoraria from Merck Serono and Horizon Pharma (formerly Nitec Pharma) and travel expenses and payment for development of educational presentations from Merck Serono. KGS received consultancy fees, honoraria and travel expenses from Merck Serono, Horizon Pharma (formerly Nitec Pharma), Novartis, Roche, Amgen, UCB, Genentech and Eli Lilly, and grant support from Merck Serono, Proctor & Gamble, Roche, GlaxoSmithKline, Amgen and Eli Lilly. SW and UR are employees of Horizon Pharma and have stock options. DM, JSz, JSu and IS reported no conflicts of interest.

Provenance and peer review Not commissioned; externally peer reviewed.

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CLINICAL STUDY PROTOCOL ADDENDUM 1

GERMANY

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
IND Number:	72,569
EudraCT Number:	2007-003508-36
Sponsor:	Nitec Pharma AG Kägenstrasse 17 4153 Reinach, Switzerland www.nitecpharma.com
Date of Protocol:	17 January 2008
Date of Protocol Addendum:	17 April 2008

SIGNATURE PAGES

SPONSORS APPROVAL OF STUDY PROTOCOL ADDENDUM

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

Stephan Witte, PhD
Chief Medical Officer

21-April-2008
Date

Achim Schäffler, PhD
EVP R&D and Technical Operations

21-April 2008
Date

DECLARATION OF INVESTIGATOR

I agree to conduct this study in accordance with the requirements of this clinical study protocol addendum 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 Coordinating Investigator

Prof. Dr. Frank Buttgereit — 22 - April 2008 (Date)

Signature of Investigator at site

Investigator — Date

Rationale for this addendum

The purpose of this addendum was to include an additional exclusion criterion for Germany, since it was advised that the administration of glucocorticoids can lead to an increase of internal eye pressure.

Summary of changes

One additional exclusion criterion was added to the clinical study protocol.

To clearly highlight the changes made, the new text has been bolded (**new text**).

Protocol Synopsis, Page 8

Original text

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 predniso(lo)ne
- 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.)

New text

Exclusion criteria:

The presence of any of the following will exclude a patient from study enrolment:

- **An existing family predisposition for glaucoma, except if a medical ophthalmological examination of intraocular eye pressure measurement reveals normal findings**
- 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 predniso(lo)ne
- 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.)

Section 4.5, Exclusion Criteria, Page 28

Original text

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 predniso(lo)ne
- 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.)

New text

4.5 EXCLUSION CRITERIA

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

- **An existing family predisposition for glaucoma, except if a medical ophthalmological examination of intraocular eye pressure measurement reveals normal findings**
- 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 predniso(lo)ne
- 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.)

CLINICAL STUDY PROTOCOL AMENDMENT 1

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
IND Number:	72,569
EudraCT Number:	2007-003508-36
Sponsor:	Nitec Pharma AG Kägenstrasse 17 4153 Reinach, Switzerland www.nitecpharma.com
Date of Protocol:	17 January 2008
Date of Protocol Amendment:	04 August 2008

SIGNATURE PAGES

SPONSORS APPROVAL OF STUDY PROTOCOL AMENDMENT

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

Stephan Witte, PhD
Chief Medical Officer

05 AUG 2008
Date

Achim Schäffler, PhD
EVP R&D and Technical Operations

05 Aug 2008
Date

DECLARATION OF INVESTIGATOR

I agree to conduct this study in accordance with the requirements of this clinical study protocol amendment 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 Coordinating Investigator

Prof. Dr. Frank Buttgereit

6.8.08
Date

Signature of Investigator at site

Investigator

Date

Rationale for this amendment

The purpose of this amendment was to make clarifications and changes to sections of text in order to make them consistent throughout the protocol, to better reflect current clinical practice, and to make some necessary administrative changes.

Summary of changes

Number of sites to be utilized changed from 40 to 45 to 50 to 55.

Changes to three exclusion criterion for clarification of the text and to better reflect current clinical practice.

Additional text regarding ongoing AEs at final visit included for consistency.

Collection and development of Hemoccult/guaiac test moved from Visit 0 to Visit 1 in study schedule.

Hemoccult/guaiac tests to be performed for safety reasons only and no longer for efficacy evaluation.

Additional text added regarding destruction of study materials for clarification.

Address of Coordinating Investigator added.

To clearly highlight the changes made, the new text has been bolded and italicized (***new text***) and any text removed is shown with strikethrough (~~old text~~).

Protocol Synopsis, Page 7

Original text

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

New text

Study Sites:
Approximately ~~40 to 45~~ ***50 to 55*** in North America and Europe

Protocol Synopsis Exclusion Criteria, Page 8

Original text

- 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 (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

New text

- Suffering from another disease, which requires glucocorticoid treatment ***during the study period***, 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~~:
    - ***Continued use of systemic glucocorticoids within 4 weeks prior to screening visit (Visit 0)***
    - ***Intermittent use of glucocorticoids within 2 weeks prior to screening visit (Visit 0). (Intermittent is defined as a maximum of 7 days treatment with a cumulative dose of ≤ 100mg prednisone or equivalent within 6 weeks prior to Visit 0)***
    - ***Joint injections within 6 weeks prior to screening visit (Visit 0)***
    - ***Topical glucocorticoids, e.g. intra-nasal or inhaled glucocorticoids must be stopped at screening visit (Visit 0)***
- Use of biologicals ***such as***: ***tumor necrosis factor α (***TNFα***)*** inhibitor***s and other compounds*** within ***5 serum half lives***~~3 months~~ prior to screening visit (Visit 0)~~, other compounds within 1 year prior to screening Visit 0~~

Study Schedule, Page 12

Original text

Randomization

		Double-blind phase			
Visit	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Week	**-1**	**0**	**2**	**6**	**12**
Collect and develop Hemoccult/guaiac Test	✓				✓

New text

Randomization

		Double-blind phase			
Visit	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Week	**-1**	**0**	**2**	**6**	**12**
Collect and develop Hemoccult/guaiac Test	~~✓~~	✓			✓

Study Schedule Footnotes, Page 13

Original text

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.

New text

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.~~ ***For ongoing AEs at final visit 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.***

Section 3.1 Study Design, Page 25

Original text

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).

New text

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~~***50 to 55*** 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 ***currently*** treated with ~~a~~ glucocorticoid***s*** ~~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).

Section 4.1 Number of Patients, Page 26

Original text

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.

New text

This sample will be obtained from approximately ~~40 to 45~~ ***50 to 55*** centers in North America and Europe. It is expected that each study site will enroll between 6 and 28 patients.

Section 4.5 Exclusion Criteria, Page 28

Original text

- 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

New text

- Suffering from another disease, which requires glucocorticoid treatment ***during the study period***, 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~~:
    - ***Continued use of systemic glucocorticoids within 4 weeks prior to screening visit (Visit 0)***
    - ***Intermittent use of glucocorticoids within 2 weeks prior to screening visit (Visit 0). (Intermittent is defined as a maximum of 7 days treatment with a cumulative dose of ≤ 100mg prednisone or equivalent within 6 weeks prior to Visit 0)***
    - ***Joint injections within 6 weeks prior to screening visit (Visit 0)***
    - ***Topical glucocorticoids, e.g. intra-nasal or inhaled glucocorticoids must be stopped at screening visit (Visit 0)***

- Use of biologicals ***such as:*** TNFα inhibitor***s and other compounds*** within ***5 serum half lives***~~3 months~~ prior to screening visit (Visit 0)~~, other compounds within 1 year prior to screening Visit 0~~

Section 5.5 Supplies and Accountability, Page 36

Original text

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.

New text

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. ***Destruction of study medication should follow the local applicable standard procedures.***

Section 7.2.3 End of Treatment, Page 43

Original text

- Document incidences and types of AEs in the CRF

New text

- Document incidences and types of AEs in the CRF
    - ***For ongoing AEs at final visit 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***

Section 7.3.1.8 Hemoccult/Guaiac Tests, Page 47

This entire section will be removed and the text placed in Section 7.3.2.3 Hemoccult/Guaiac Tests (see below). As a consequence, Section 7.3.1.9 Diary will now become Section 7.3.1.8.

Section 7.3.2.3 Hemoccult/Guaiac Tests, Page 51/52

Original text

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.

New text

~~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.~~

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.

Section 14.2, Declaration of Investigator, Page 72

Original text

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

New text

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

Charité - Universitätsmedizin Berlin
The Medical Department, Division of Rheumatology
Chariteplatz 1
10117 Berlin, Germany

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
IND Number:	72,569
EudraCT Number:	2007-003508-36
Date of Issue:	17 January 2008
Sponsor:	Nitec Pharma AG Kägenstrasse 17 4153 Reinach, Switzerland www.nitecpharma.com

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Study Number
NP01-007

17 January 2008

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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 predniso(lo)ne
- 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 (DAS)28 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.

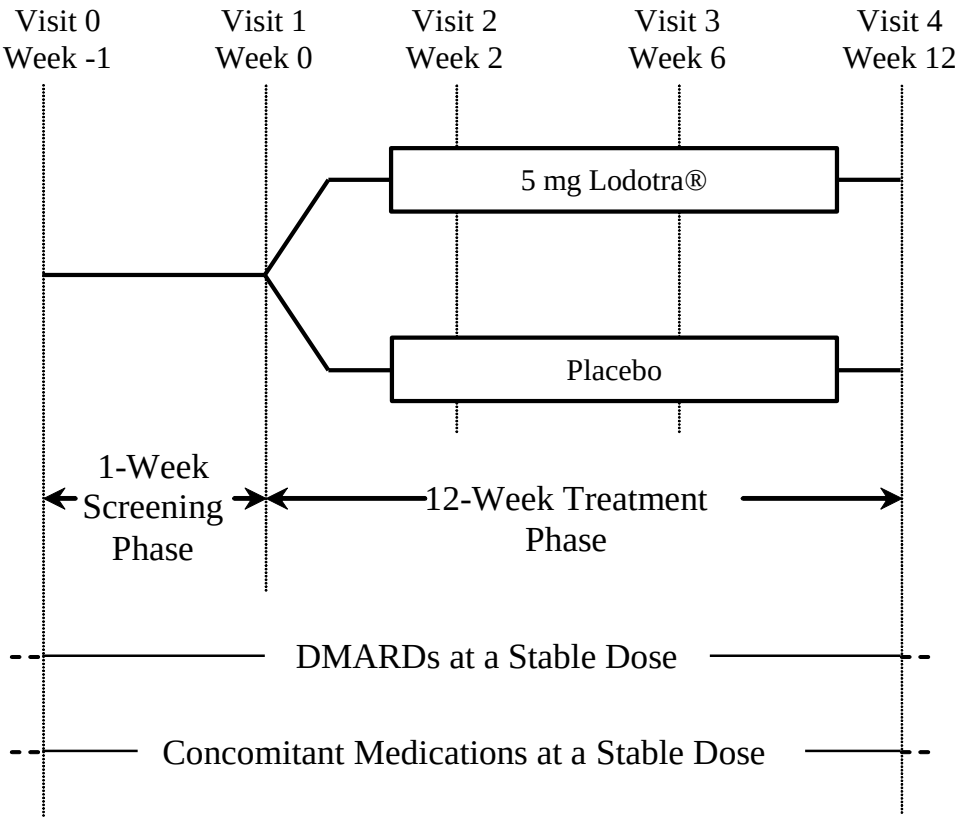
The relative change in morning stiffness and the absolute changes in the ACR core set measures will be analyzed using analysis of covariance (ANCOVA) with treatment and (pooled) sites as factors and the relevant baseline score as a covariate.

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



STUDY SCHEDULE

Randomization

		Double-blind phase			
Visit	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Week	**-1**	**0**	**2**	**6**	**12**
Informed consent	✓				
Inclusion and exclusion criteria	✓				
Demographic and baseline characteristics	✓				
Medical history	✓				
Previous medication [a]	✓				
Concomitant medication	✓	✓	✓	✓	✓
Physical examination	✓				✓
Vital signs	✓	✓	✓	✓	✓
Rheumatoid Disease Status [b]	✓	✓	✓	✓	✓
Safety laboratory [c]	✓				✓
Inflammatory cytokines (IL6 and TNFα)	✓				✓
Urinalysis [c]	✓				✓
Dispense Hemoccult/guaiac Test [d]	✓	✓		✓	
Collect and develop Hemoccult/guaiac Test	✓				✓
Dispense study medication	✓	✓	✓	✓	
Fix appointment for next visit	✓	✓	✓	✓	
Dispense, collect and review study diaries [e]	✓	✓	✓	✓	✓
Adverse events [f]		✓	✓	✓	✓
Assess compliance		✓	✓	✓	✓
QoL questionnaire (SF-36)		✓			✓
Fatigue questionnaire (FACIT-F)		✓			✓
Randomization criteria		✓			
Randomization and fax confirmation		✓			
Collect unused medication		✓	✓	✓	✓
Switch to immediate release predniso(lo)ne					✓

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:

ACR20 is evaluated using 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), acute-phase reactant [ESR or CRP] in blood.

DAS28 is evaluated using tender joint count, swollen joint count, acute-phase reactant [ESR] in blood, patient's global assessment of disease activity.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ACR	American College of Rheumatology
AE	Adverse Event
ALAT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
ASAT	Aspartate Aminotransferase
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
DAS	Disease Activity Score
DMARDs	Disease Modifying Anti-Rheumatic Drugs
EC	Ethics Committee
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy- Fatigue
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI	Functional Disability Index of the Health Assessment Questionnaire
ICH	International Conference on Harmonization
IL-6	Interleukin-6
IR	Immediate-Release
IRB	Institutional Review Board
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities

MR	Modified-Release
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PP	Per-protocol
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase (=ASAT)
SGPT	Serum Glutamic Pyruvic Transaminase (=ALAT)
SF-36	Short Form 36 (Quality of Life)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TNFα	Tumor Necrosis Factor α
VAS	Visual Analogue Scale
ULN	Upper Limit of Normal

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 predniso(lo)ne, 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 predniso(lo)ne 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 predniso(lo)ne
- 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 predniso(lo)ne 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.

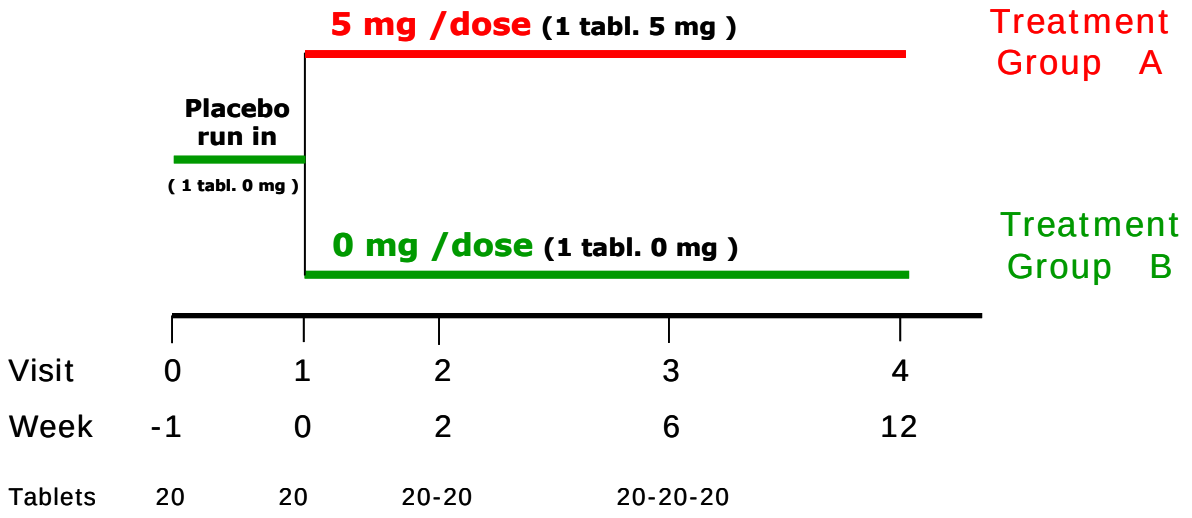
If a patient becomes pregnant while enrolled in the trial, the investigational product should be discontinued, and the patient withdrawn from the study. Further treatment should be addressed on a case-by-case basis with the treating physician and the investigator.

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



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

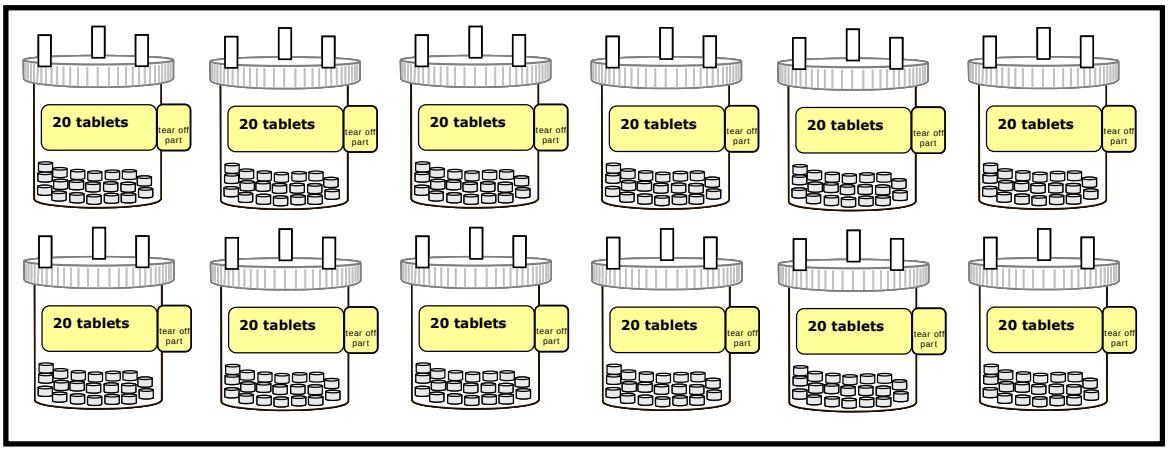
Study medication is always packed in white round polyethylene containers (bottles) of 40 mL containing 20 tablets each. The push-fit tamper-evident caps are designed to ease the opening procedure for users with special needs. The cap has three fixation points on the top to enable opening assisted by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

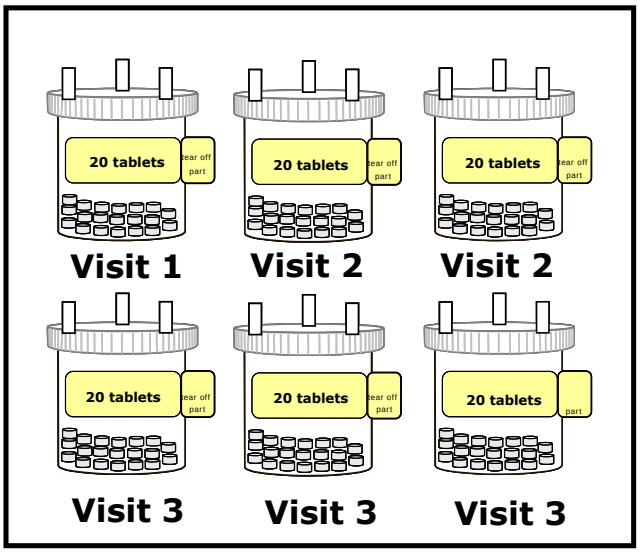
5.1.2.3 Screening boxes

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



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 × 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 predniso(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 predniso(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 predniso(lo)ne. Predniso(lo)n 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

	Blood volume (in mL) withdrawn from each patient during the study					
Visit	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Total**
Week	**-1**	**0**	**2**	**6**	**12**	
Safety laboratory (biochemistry and hematology)	10	-	-	-	10	20
ESR	2	2	2	2	2	10
CRP	1	1	1	1	1	5
IL-6 and TNFα	2	-	-	-	2	4
Total	15	3	3	3	15	39

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:

$$\begin{aligned} \text{DAS28} &= 0.56 * \sqrt{(\text{number of tender joints})} \\ &+ 0.28 * \sqrt{(\text{number of swollen joints})} \\ &+ 0.70 * \ln(\text{ESR, 1st hour})\ [\text{mm}] \\ &+ 0.014 * \text{patient's global assessment of disease activity (VAS)}\ [\text{mm}] \end{aligned}$$

- 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 α=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 χ^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 α=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

21-JAN-2008
Date

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

22 JAN 2008
Date

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

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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:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

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

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

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

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c Lifting or carrying groceries	☐1	☐2	☐3
d Climbing several flights of stairs	☐1	☐2	☐3
e Climbing one flight of stairs	☐1	☐2	☐3
f Bending, kneeling, or stooping	☐1	☐2	☐3

g Walking more than a mile..... ☐1 ..... ☐2 ..... ☐3

h Walking several hundred yards..... ☐1 ..... ☐2 ..... ☐3

i Walking one hundred yards..... ☐1 ..... ☐2 ..... ☐3

j Bathing or dressing yourself..... ☐1 ..... ☐2 ..... ☐3

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

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

a Cut down on the amount of time you spent on work or other activities ☐1..... ☐2 ..... ☐3..... ☐4..... ☐5

b Accomplished less than you would like ☐1..... ☐2 ..... ☐3..... ☐4 ..... ☐5

c Were limited in the kind of work or other activities ☐1..... ☐2 ..... ☐3..... ☐4..... ☐5

d Had difficulty performing the work or other activities (for example, it took extra effort) ☐1..... ☐2 ..... ☐3..... ☐4..... ☐5

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities <u>less carefully</u> than usual	☐1	☐2	☐3	☐4	☐5

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

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i 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.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

- **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:

DRESSING & GROOMING	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
Are you able to:				
- Dress yourself, including tying shoelaces and doing up buttons?	_____	_____	_____	_____
- Wash your hair?	_____	_____	_____	_____
RISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
- Cut up your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

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

_____ Walking stick

_____ Walking frame

_____ Crutches

_____ Wheelchair

_____ Aids used for dressing (button hook, zip-puller, long-handled shoe horn, etc.)

_____ Specially adapted utensils (such as for eating and cooking)

_____ Specially adapted chair

_____ Other (Please specify:_____)

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

_____ Dressing and Grooming

_____ Rising

_____ Eating

_____ Walking

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

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
HYGIENE				
Are you able to:				
- Wash and dry your body?	_____	_____	_____	_____
- Have a bath?	_____	_____	_____	_____
- Get on and off the toilet?	_____	_____	_____	_____
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 seat

_____ Jar opener (for jars previously opened)

_____ Bath rail

_____ Long-handled appliances for reaching things

_____ 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

_____ Reaching

_____ Gripping and opening things

_____ 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 0 _____ SEVERE PAIN 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 <u>during the past 7 days.</u>**

	PHYSICAL WELL-BEING	**Not at all**	**A littl e bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness.....	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	**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.**	☐				
GS7	I am satisfied with my sex life.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE 1	I feel sad.....	0	1	2	3	4
GE 2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE 3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE 4	I feel nervous.....	0	1	2	3	4
GE 5	I worry about dying.....	0	1	2	3	4
GE 6	I worry that my condition will get worse.....	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling..	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued.....	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired.....	0	1	2	3	4
An4	I have trouble finishing things because I am tired.....	0	1	2	3	4
An5	I have energy.....	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day.....	0	1	2	3	4
An 12	I am too tired to eat.....	0	1	2	3	4

An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do.....	0	1	2	3	4
An 16	I have to limit my social activity because I am tired.....	0	1	2	3	4

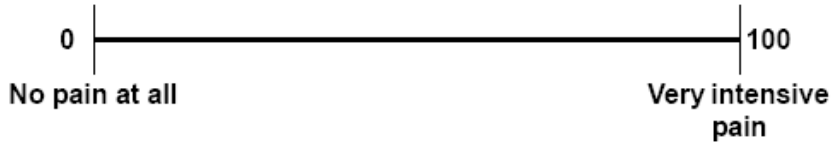
- **Questionnaire forming part of the Disease Activity Score (DAS)**

Rheumatoid Arthritis Activity: Visual Analogue Scale Measurements

Date of VAS Assessments: Day Month Year 2 0 0

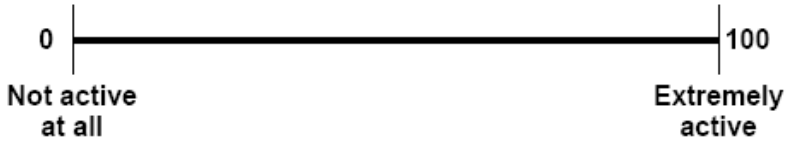
Subject's Pain Assessment for Rheumatoid Arthritis

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



Subject's Global Assessment of Disease Activity

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



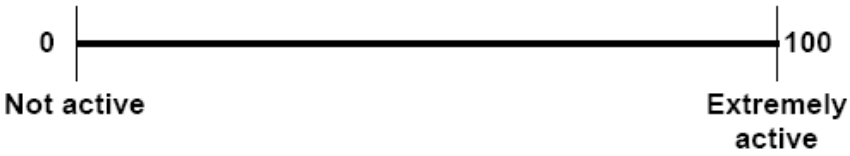
Rheumatoid Arthritis Activity: Visual Analogue Scale Measurements (continued)

Date of **Physician's** VAS Assessments:

Day	Month	Year
		2 0 0

Physician's Global Assessment of Disease Activity

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



Physician's Global Assessment of Disease Activity Measurement ___ mm

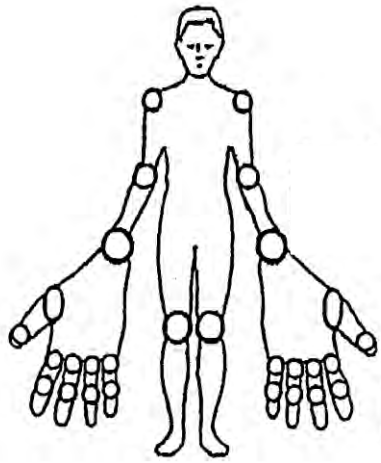
(Using a ruler, measure in centimeters to one decimel place from the left hand side of the 100mm scale to the mark made by the subject.)

APPENDIX II: 28 JOINT GRAPH

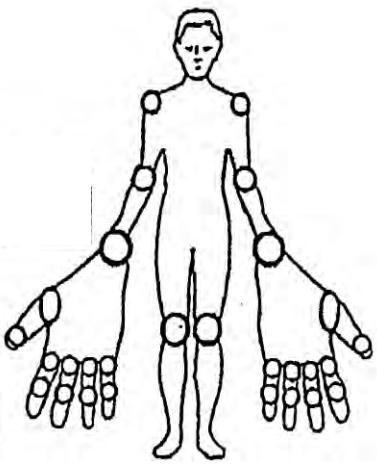
DAS 28

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

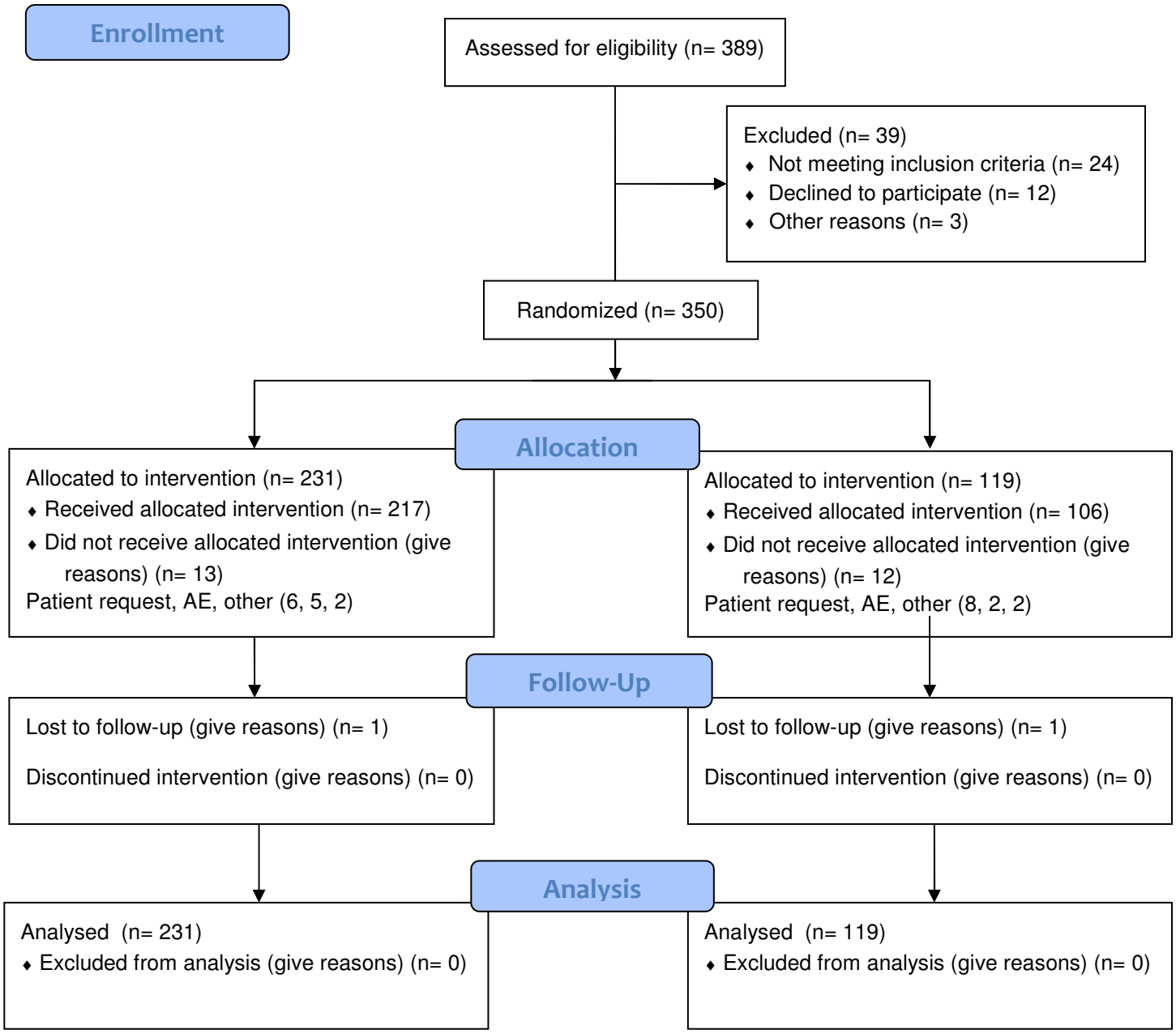
Tender joints



Swollen joints



CONSORT 2010 Flow Diagram



STATISTICAL ANALYSIS PLAN

Final Version 1.0
17 July 2009

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

The CAPRA-2 Study

Protocol Number: NP01-007
(17 January 2008
Amendment 1: 04 August 2008)

SPONSOR
Nitec Pharma AG
Kägenstrasse 17
4153 Reinach, Switzerland
www.nitecpharma.com

Statistical Analysis Plan Signature Page

Final Version 1.0, dated 17 July 2009

Sponsor: Nitec Pharma AG

Protocol: NP01-007

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

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Director Clinical Research

Date 20 July 2009

Approver
Stephan Witte, PhD
Chief Medical Officer

Date 20 July 2009

TABLE OF CONTENTS

LIST OF ABBREVATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology
AE	Adverse Event
ANCOVA	Analysis of covariance
CRF	Case Report Form
CRP	C-reactive protein
DAS	Disease activity score
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACIT-G	Functional Assessment of Chronic Illness Therapy-General
HAQ-DI	Functional Disability Index of the Health Assessment Questionnaire
ICH	International Conference on Harmonisation
IL-6	Interleukin-6
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intention-to-treat
MR	Modified-Release
PP	Per-Protocol
PT	Preferred Term
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	Short Form 36
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TNFα	Tumor Necrosis Factor α
VAS	Visual analogue scale

1 INTRODUCTION

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in this Phase III, Randomized Multi-Center, Double-Blind, Placebo-Controlled Study of a New Modified-Release Tablet Formulation of Prednisone (Lodotra®) in Patients with Rheumatoid Arthritis (RA).

The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines [1, 2] and in reference to Protocol NP01-007 (17 January 2008) and its amendment (04 August 2008)

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is

- to evaluate if 12 weeks of treatment with 5 mg modified-release (MR) prednisone (Lodotra®) administered in the evening is superior to placebo in terms of the American College of Rheumatology (ACR)20 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 from baseline

Additional secondary objectives of this study are to determine whether treatment with 5 mg Lodotra® administered in the evening is superior to placebo in terms of:

a) Efficacy:
- Time to Response (ACR20 criteria)
- ACR50
- ACR70
- Disease Activity Score (DAS)28 score at each visit
- European League Against Rheumatism (EULAR) response criteria
- Morning stiffness at each visit
  - ✓ Relative (to baseline) reduction of duration of morning stiffness
  - ✓ Absolute reduction of duration of morning stiffness
  - ✓ Severity of morning stiffness
  - ✓ Reoccurrence of stiffness during day
- Individual ACR20 and DAS28 criteria (ACR Core test)
  - ✓ Tender joint count
  - ✓ Swollen joint count
  - ✓ Patient's assessment of pain - assessed using 100mm visual analogue scale (VAS)

- ✓ Patient's global assessment of disease activity - assessed using 100mm VAS
- ✓ Physician's global assessment of disease activity - assessed using 100mm VAS
- ✓ Functional disability index of the Health Assessment Questionnaire (HAQ-DI)
- ✓ Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as acute-phase reactants

- Requirements for additional analgesics
- Occurrence of pain in morning and evening
- Inflammatory cytokines at each visit (Interleukin-6 (IL-6) and tumor necrosis factor α (TNFα))
- Quality of life
  - ✓ Health Assessment Questionnaire (HAQ-DI, as part of ACR20)
  - ✓ Short Form 36 (Quality of Life; SF-36)
  - ✓ Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F] – 13 items questionnaire)

b) Safety

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

3 STUDY DESIGN

This is a randomized, multi-centre, double-blind, parallel-group, placebo-controlled 13 week study comparing evening administration of 5 mg Lodotra® to placebo in patients with RA. It was planned to randomize a total of 294 patients in 70 to 80 centers in North America and Europe.

Patients 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 (see flow chart on page 11 and 12 of the protocol). 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 x 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 prednisol(lo)ne. Overall duration of the study is planned to be one and a half years.

4 CHANGES FROM PROTOCOL IN STUDY CONDUCT OR STATISTICAL ANALYSIS

- DAS28 will be analyzed using CRP value instead of ESR, as CRP is analyzed by a central laboratory.
- Age class and gender were added to the primary analysis as covariates.
- Nested effect of the pooled sites within geographical region and its interaction with the treatment was added to ACR20 sensitivity analysis.
- Duration of morning stiffness will be analyzed using Hodges Lehmann due to the non-normality of the data.
- DAS28 will be analyzed by an analysis of covariance (ANCOVA) with treatment, nested effect of the pooled sites within region [Pooled Site(Region)] (see section 8.3.1.2) as factor and a term for interaction between the nested effect and treatment; the nested effect of the pooled sites within region factor will be analyzed as a random effect.
- Urine CTX will be analyzed separately from the safety lab data as it is a biomarker of the cartilage or bone degradation.

5 ANALYSIS POPULATIONS

Three analysis populations will be defined for this study as outlined below.

The primary analysis population for efficacy and safety will be the safety population. The primary and key secondary endpoints will also be analyzed using the modified intention-to-treat (mITT) and Per Protocol (PP) population.

ICH E9 guideline suggests that the analysis of the primary endpoint should be analyzed according to the treatment to which patients were actually randomized (modified ITT population). However, in this study approximately 5% of patients were assigned to a treatment that was not consistent with the intended randomization schedule due to blinded errors of study personnel (i.e. distribution of medications in the wrong order). For these reasons, analyzing the primary endpoint according to the patients actually received (safety population) should not be biased and should reflect the true comparative activity of the agents.

To assess the treatment effect using different assumptions from those in the mITT and safety analyses, the primary efficacy (ACR20) and key secondary (relative change in

duration of morning stiffness) variables will also be analyzed using the per-protocol (PP) population. All safety analyses will be based on the safety population.

5.1 SAFETY POPULATION

The Safety Population will include 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.

5.2 MODIFIED INTENTION-TO-TREAT POPULATION

The modified intention-to-treat (mITT) population will include 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 intended to be randomized to.

According to the study protocol, the treatment kits for patients were packed into "site shipper" boxes that contained one randomization block each. These were then distributed to sites. Each treatment kit is identified with a unique, predefined number (= randomization number). A list of treatment kits sent to each site will be provided by the drug distributor to determine the intended randomization schedule. The investigators then allocate the lowest kit number to the next patient eligible for randomization. If a treatment kits is damaged or out of date, the sequencing will be adjusted accordingly. All patients randomized out of order will be presented in a listing.

5.3 PER PROTOCOL POPULATION

The Per Protocol (PP) population will include all patients who were randomized, treated with study medication and did not have a major protocol deviation. Major protocol deviations leading to exclusion from the PP population will be finalized prior to unblinding during the blind data review meeting. The per-protocol population will be based on the mITT population.

6 EFFICACY ANALYSIS VARIABLES

6.1 Primary Efficacy variable

The primary efficacy variable is the ACR20 responder rate after 12 weeks of double-blind treatment with the study medication. Responders are defined as those whose improvement from baseline to endpoint (12 weeks) fulfils 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 global assessment of disease activity (VAS)
    - HAQ-DI

- CRP or ESR as acute-phase reactant. CRP will be used. If the CRP result is not available then the ESR result will be used to calculate the ACR20 responder status

6.2 Secondary Efficacy variable

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

Additional secondary efficacy variables are as follows:

- ACR20 response rate at week 2 (visit 2) and week 6 (visit 3)
- ACR50 response rate at week 2 (visit 2), week 6 (visit 3) and week 12 (visit 4), responders are defined as per ACR20 but using 50% reduction instead of 20%
- ACR70 response rate at week 2 (visit 2), week 6 (visit 3) and week 12 (visit 4) , responders are defined as per ACR20 but using 70% reduction instead of 20%
- Time to Response based on ACR20 criteria
- Change from baseline in DAS28 at each visit: DAS28 is a score aggregating data of 28 joints, and is calculated as:

$$\begin{aligned} DAS28 = {} & 0.56 \times \sqrt{(\text{number of tender joints})} \\ & + 0.28 \times \sqrt{(\text{number of swollen joints})} \\ & + 0.36 \times \ln(CRP + 1) \\ & + 0.014 \times \text{patient's global assessment of disease activity} \\ & + 0.96 \end{aligned}$$

  Where CRP is expressed in mg/L and patient's global assessment of disease activity (VAS) is expressed in mm. If the CRP result is missing, DAS28 will be computed using the following formula.

$$\begin{aligned} DAS28 = {} & 0.56 \times \sqrt{(\text{number of tender joints})} \\ & + 0.28 \times \sqrt{(\text{number of swollen joints})} \\ & + 0.70 \times \ln(CRP) \\ & + 0.014 \times \text{patient's global assessment of disease activity} \end{aligned}$$

- EULAR response rate at each visit: patients will be classified as patients with good, moderate or no response based on their change in DAS28[3].
- Relative reduction (%) and absolute reduction of morning stiffness between baseline and other study visits
- Relative reduction (%) and absolute reduction from baseline of morning stiffness at each week.
- Change from Baseline in Severity of morning stiffness at each visit: 100 mm VAS
- Change from baseline in terms of reoccurrence of stiffness during day (while performing routine activities). Reoccurrence of Stiffness during the day will be assessed as the percentage of days with reoccurrence of stiffness over the last 7 days prior to each visit (if 4 or more responses are missing the percentage will be set to missing)

- Change from baseline in tender and swollen joint counts at post-baseline study visit: 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.
- Change from baseline in patient assessment of the pain intensity at each visit (100 mm VAS)
- Change from baseline in physician's and patient's global assessments of disease activity at each visit (100 mm VAS)
- Change from baseline in HAQ-DI at each visit: 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.
- Change from baseline in inflammatory parameters at each visit: CRP, ESR, TNFα and IL-6
- Change from baseline in the occurrence of pain in morning and evening (100 mm VAS) will be computed as the change in percentage of occurrence of pain in morning/evening over the last 7 days prior to each visit (if 4 or more responses are missing the percentage will be set to missing)
- Change from baseline in use of additional analgesics (no/yes) will be computed as the change from baseline in percentage of days with the event over the last 7 days prior to each visit (if 4 or more response are missing the percentage will be set to missing)
- The use of additional analgesic will also be assessed as the number of days with additional analgesic during the first 12 weeks of double-blind treatment period.
- Change from baseline in each domain of the Short Form 36 questionnaire (Quality of Life; SF-36) and for the mental and physical component scores.
- Change from baseline in the FACIT fatigue questionnaire: this is a subset of the FACIT-F questionnaire comprising 13-items.

6.3 EFFICACY ASSESSMENTS

Efficacy data is based on:

- Individual ACR20, ACR50, ACR70 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), and analgesics (painkillers)
- SF-36 questionnaire
- FACIT-F questionnaire (13 items fatigue section)

6.3.1 ACR20, ACR50, ACR70

The following table shows how the response for the different cut-off of the ACR criteria will be assessed based on the responses for each parameter of the ACR.

	≥XX% improvement achieved?							
Scenario	**SJC**	**TJC**	**C1**	**C2**	**C3**	**C4**	**C5**	**ACRXX responder**
1	N	Y/N/M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	N
2	Y/N/M	N	Y/N/M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	N
3	Y	Y	Y	Y	Y	Y/N/M	Y/N/M	Y
4	Y	Y	N	N	N	Y/N/M	Y/N/M	N
5	Y	Y	M	M	M	Y/N/M	Y/N/M	M
6	Y	Y	Y	Y	N	M	M	M
7	Y	Y	Y	N	N	M	M	M
8	Y	Y	Y	Y	N	N	M	M
9	Y	M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	M
10	M	Y	Y/N/M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	M
11	M	M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	Y/N/M	M

Key: Y is ≥XX% improvement achieved; N is <XX% improvement not achieved; M is Missing; SJC=Swelling; TLC=Tenderness; C1-C5 are the 5 remaining ACR components (Patient assessment of pain, patient's global assessment of status disease, physician's global assessment of disease activity, HAQ-DI and CRP or ESP) in any order.
XX represents the different cut-off: 20, 50 and 70.

6.3.2 Patient's and Physician's global assessment of disease activity

Disease activity is 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.

6.3.3 Patient's assessment of pain

Maximum intensity of pain is documented and intensity is assessed by marking the respective value on a 100 mm VAS (with the endpoints 0=no pain at all and 100=very intensive pain). The current state of pain assessed during the visit is used for the ACR20 assessment, pain at morning and evening is also collected using the same method in the patient's diary.

6.3.4 Tender joint count

The following 28 joints (14 left, 14 right) are assessed for tenderness: shoulder, elbow, wrist (radiocarpal, carpal and carpometacarpal are collectively designated wrist), metacarpophalangeal I-V, thumb interphalangeal, proximal interphalangeal II-V, knee. 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 manoeuvre.

6.3.5 Swollen joint count

The same 28 joints as mentioned above in section 6.3.3 are assessed 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.

6.3.6 Functional disability index of HAQ-DI

The HAQ-DI includes eight blocks of questions (dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities) 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 (0=none, 1=some difficulty, 2=great difficulty, 3=not able to perform at all).

The HAQ-DI score is the average across the maximum score in each category. The HAQ-DI requires at least 6 of the categories to be non-missing. Individual questions within a category are not imputed. Therefore the maximum score in each category is based on non-missing questions, and a category score is missing when all questions within a category are missing. The scoring will be adjusted with regards to the use of devices, aids and/or help from a person to perform the task. Details of computation are provided in the technical specification.

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

6.3.7 EULAR

EULAR criterion is based on DAS28 and the following characterization of the disease status and its change from baseline.

	Visit		
Baseline	**Improvement > 1.2**	**0.6 < Improvement ≤ 1.2**	**Improvement ≤ 0.6**
DAS28 ≤ 3.2	Good response	Moderate response	No response
3.2 < DAS28 ≤ 5.1	Moderate response	Moderate response	No response
DAS28 > 5.1	Moderate response	No response	No response

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

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

- ESR is assessed (in mm/h) by measuring the sedimentation rate in the first hour after withdrawal of blood at each visit at local laboratories using routine local standard methods and equipment. This data is used for the assessment of ACR20.
- CRP (mg/L) is analyzed from 1 mL serum by a central laboratory and is used for the determination of ACR20 and DAS28.
- IL-6 (pg/mL) and TNFα: the blood samples for the determination of these parameters are processed and stored according to protocols provided by the central laboratory
- Urine CTX

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.

CRP, IL-6 and TNFα will be blinded by the central lab until database lock and unblinding of the treatment group.

6.3.9 SF-36

The SF-36v2 Quality of Life questionnaire consists of 36 generic health questions. There are 8 health domains of the questionnaire, each of which will be summarized (Physical functioning score (10 items), Role-physical score (4 items), Bodily pain (2 items), General health score (5 items), Vitality score (4 items), Social functioning score (2 items), Role-emotional score (3 items), and Mental health score (5 items)). Additional details of computation are provided in the technical specification.

The answers to each question (recoded as necessary) are summed for each subject at each visit, within each of the 8 domains. If an item is missing, it should be imputed as the mean of the non-missing items in its domain for the purposes of calculating the domain score. Note that this imputation applies only to the calculation of the domain scores; imputation of individual item scores will not be presented. At least 50% of the item scores in a domain must be non-missing to calculate the domain score, otherwise the domain score is set to missing.

The resulting score for each domain (after the imputation described above) is then standardized, to obtain values ranging from 0 to 100, with higher values indicating a better quality of life.

$$\text{Standardised Score} = \left(\frac{\text{Sum - Lowest possible score}}{\text{Possible raw score range}} \right) \times 100$$

In addition, the physical and mental component score will be computed using the US weighting scales. Details are provided in the technical specifications.

6.3.10 Functional assessment of chronic illness therapy-fatigue (FACIT-F)

The Fatigue questionnaire (subset of the FACIT-F questionnaire) is used to assess the impact of patient's fatigue on their daily activity and function. It is a 13 item questionnaire which is to be completed by the patient on a 5 point grading system (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). The overall score is the sum of the average of the subscales. Details of computation are provided in the technical specification.

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

6.3.11 Diary

Patients were instructed to enter their data twice daily. Reoccurrence of stiffness during the day, occurrence of pain in the morning and evening and use of analgesics will be analyzed as a percentage of days with the event over the last 7 days prior to or on each visit (if 4 or more response are missing the percentage will be set to missing). Other parameters, VAS scales, duration of morning stiffness, will be computed as the mean over the last 7 days prior or on each visit. The diary data will be slotted to match the CRF visit date.

If the patient recorded that no pain was experienced and the corresponding VAS score is missing it will be set to 0 (i.e. no pain).

Duration of morning stiffness will be summarized for each week, weeks being defined from the day of first dose. All assessments within a week will be computed as per the same rules as above.

Parameters to be entered by the patients in the diary are given in the section 7.3.1.9 of the protocol.

7 SAFETY ENDPOINTS

Safety will be assessed by evaluation of the following variables: adverse events, serious adverse events (SAEs), laboratory tests (hematology, urinalysis and serum chemistry), physical examination and vital signs.

Hemoccult/guaiac tests were performed prior to randomization at Visit 0 and prior to the end of treatment at Visit 4.

8 STATISTICAL EVALUATION

8.1 SAMPLE SIZE AND POWER

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 χ^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 α=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 standard deviation (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%.

8.2 INTERIM ANALYSIS

No interim analysis is planned for this study.

8.3 STATISTICAL METHODS

8.3.1 General Statistical Methodology

8.3.1.1 General Convention

General algorithms, imputations and conventions that will generally apply to program derivations of the data as required to perform the proposed summary tabulations, individual patient data listings, and figures will be detailed in a separate document, which will be signed off prior to 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 or the visit day (whichever occurred first). Data from the diary will not be analyzed if recorded more than 3 days after the last dose of study drug.

Time points in the summaries will be the planned relative times as shown in the CRF.

All efficacy and safety variables will be summarized by treatment groups using descriptive statistics (n, 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).

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.

Percentages will be presented to one decimal place throughout.

All statistical tests will be two-sided and performed at the 5 % significance level. 95% confidence intervals will be provided where appropriate. Data will be summarized by visit.

All dates will be displayed in DDMMMYYYY format. Visits will be referred to as shown in the protocol: "Screening (V0)", "Baseline (V1)", "Visit 2", "Visit 3" and "Visit 4"

All analyses will be carried out using SAS® Version 8.02 or later on Windows 2000 or later.

8.3.1.2 Pooled Sites

As it is expected to have between 70 and 80 sites, and the sensitivity analysis for the primary endpoint is analyzed using a logistic regression with a nested effect of the sites within the region (defined as USA/Canada and Europe) and an interaction between the treatment and the nested effect, in order to estimate the difference in treatment each cell needs to have at least one observation. Therefore sites will be pooled together and country will be pooled into geographic area; when pooling sites, whenever possible sites within a country will be pooled together. Since the randomization is done at a site level, in order for the model to still be convergent after unblinding, it is expected that a minimum of 12 patients in each pooled sites (with at least 6 responders and 6 non-responders) will be sufficient. The pooling will be documented prior to the unblinding of the study.

8.3.2 Handling of Missing and Incomplete Data

8.3.2.1 Primary endpoint

Each patient will be defined as a responder or non-responder at visit 4 according to the ACR20 criteria. If the response is missing at visit 4 the following imputation schemes will be used:

For the safety population, the primary analysis will consist in imputing all missing assessments at visit 4 as non responder. As a sensitivity analysis, the missing assessments will be imputed conditionally to the completion of the study by the patient, i.e. if a patient discontinued prematurely, the ACR20 will be imputed as non-responder, while patients who completed the study but have a missing assessment for ACR20 at visit 4 will not be imputed. Analysis for the observed case only will be presented as a secondary sensitivity analysis. It is assumed that final efficacy assessments will be available and complete for all PP patients.

At any visit, if the CRP result is not available then the ESR result will be used to compute the ACR20 criteria.

8.3.2.2 Secondary endpoints

8.3.2.2.1 Diary data

Assessments of diary data will be based on the last 7 days prior to each visit. If more than 4 assessments during this 7 days period are missing, the assessment will be set to missing. In this case only, a LOCF (last observation carried forward) method will be applied for imputing missing assessments and will consist of taking the last 7 non-missing entries on the diary data prior to that visit. If strictly less than 3 assessments are available using the LOCF, the value will be set to missing.

8.3.2.2.2 CRF data

LOCF methodology will be used to impute missing assessments. If the assessment at visit 2 is missing it will not be imputed. If the visit 3 assessment is missing it will be imputed by the visit 2 assessment. If the visit 4 assessment is missing it will be imputed by the visit 3 assessment Missing subscale or item results will not be imputed, only a final score or response will be imputed if missing.
For ACR20, the worse case (as defined in section 8.3.2.1) will be applied at visit 2 and 3, in addition the worse case conditional to withdrawal will be applied at visit 3 i.e. if a patient withdrew (whatever the reason) before visit 3, he will be considered as a non-responder.

8.3.2.2.3 Time to Response (ACR20)

If a response is observed at any post-baseline visit where the assessment has been made less than 3 days after the last dose then the time to response will be computed from the date of first known as a responder.

If no response (assessment missing or "non-responder") was observed before withdrawal or last dose (+ 3 days) or visit 4, the patient data will be censored at the date of last dose + 3 days or date of withdrawal or date of visit 4 (whichever occurred first).

8.3.2.2.4 Inflammatory parameters

The LOCF will be using the unscheduled visit result. Baseline will be defined as the last non-missing results prior or on the date of first dose. In the summary table baseline summary will be based on lab result at visit 1 and change from baseline using the baseline result (as defined above) for each visit.

8.3.2.2.5 Last dose

If the last dose is missing, it will not be imputed and all the data will be analyzed.

8.3.2.2.6 Safety laboratory parameters

If a result is reported as < lower limit of quantification, it will be analyzed as half the value of the lower limit of quantification, and the minimum value in the summary table will show the analyzed value (i.e. half the value of the lower limit of quantification).

If a result is reported as > upper limit of quantification, it will be analyzed as the value of the upper limit of quantification, and the maximum value in the summary table will show the analyzed value (i.e. the upper limit of quantification).

8.3.3 Patient Disposition

A complete accounting of patient allocation will be tabulated overall and by treatment group. The patient data will be summarized and presented for each treatment group

- All patients who signed the informed consent form
- Number of randomized patients
- Number and percentage of patients included in each population i.e. Safety, Modified ITT and PP
- Number and percentage of patients in the Modified ITT with protocol violations leading to exclusion from the PP population
- Number and percentage of patients who enrolled, who completed the study, and who prematurely withdrew. The reasons for premature withdrawal will also be summarized. Supportive listings will be provided.

Inclusion and exclusion criteria at Visit 0 before receiving screening medication, and randomization criteria at Visit 1 before receiving Lodotra® or placebo will also be listed.

8.3.4 Demography and Baseline Characteristics

All demographic variables (gender, age, race, ethnic origin and BMI) and baseline characteristic data such as medical and disease history: duration of RA, age at onset of RA, previous and concomitant illness recorded at the screening visit will be summarized by treatment group.

Supportive listings will be provided.

8.3.5 Treatment Compliance and Exposure

Patient compliance to study medication will be calculated for each visit. Assessment will be based on tablets dispensed/returned dates recorded in the compliance page of the CRF. Compliance per visit will be calculated as follows:

$$\frac{\text{Number of tablets dispensed - Number of tablets returned}}{\text{(date of visit - date of previous visit)}} \times 100$$

If the visit date occurred after the date of last dose, the date of last dose + 1 will be used in the above formula.

Overall compliance will be calculated as follows:

$$\frac{\text{Number of tablets dispensed - Number of tablets returned}}{\left(\text{date of last dose - date of first dose}\right)+1}\times 100$$

Exposure per visit will be calculated as follows:

$$\left(\text{date of visit - date of previous visit}\right)$$

If the visit date occurred after the date of last dose the date of last dose + 1 will be used in the above formula.

Overall Exposure to study treatment will be calculated as follows:

$$\left(\text{date of last dose - date of first dose}\right)+1$$

Compliance and exposure will be summarized overall and by visit for each treatment group for the Safety population. Supportive listings will also be provided.

If the number of tablets returned is missing (or none have been collected by the investigator) it will be assumed for the compliance that all the tablets were taken by the patient.

8.3.6 Efficacy Analysis

The primary efficacy analysis will be based on the safety population. This primary analysis and key secondary variable (reduction in duration of morning stiffness) will also be repeated for the mITT and the PP populations. All efficacy variables will be summarized by treatment groups 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.

8.3.6.1 Primary Efficacy Analysis

The primary efficacy analysis of the ACR20 responder status at the visit 4 (week 12) endpoint will be tested using a logistic regression model with treatment and geographic area (see section 8.3.1.2), age category (less or equal than median age or above the median) and gender as factors with a two-sided significance level of α=0.05 for the safety population. All imputation schemes will be analyzed.

In order to evaluate the consistency of results across the different study sites, the logistic regression analysis will be repeated:

- First, with treatment as factor and pooled sites as a nested effect of geographic region as factors and with a treatment-by-the nested effect interaction term included in the model.

- Secondly, with treatment and geographic region as factors and with a treatment-by-region interaction term included in the model (where region is defined as USA/Canada versus Europe).

For the evaluation of the robustness of results the primary efficacy analysis will be repeated for the mITT and PP populations. Odds ratios for the difference between treatments and the associated 95% confidence interval, as well as the difference in proportion and its associated 95% confidence interval will be presented for each population. The difference in proportion will not be adjusted.

A SAS code similar to the one below will be used for the primary endpoint analysis.

proc genmod data=*dataset*;
class treat region agegrp gender;
model responder = treat region agegrp gender / link=linkc dist=binomial type3;
lsmeans treat / diff CL;
run;

The interaction between treatment and pooled sites nested within region will be tested as follows:

proc genmod data=*dataset*;
class treat region pooledsite;
model responder = treat pooledsite(region) treat* pooledsite(region) /
link=linkc dist=binomial type3;
lsmeans treat / diff CL;
run;

The interaction between treatment and region will be tested as follows:

proc genmod data=*dataset*;
class treat region;
model responder = region treat* region /
link=linkc dist=binomial type3;
lsmeans treat / diff CL;
run;

where: *treat*: treatment
region: geographic region
pooledsite: pooled sites
agegrp: age group (below or equal the to age median or above the age median)
responder: responders those who met ACR20 criteria
non-responders: those who does not meet ACR 20 criteria
linkc: logit for the odds ratio estimation and identity for the confidence interval of the difference in proportion

8.3.6.2 Secondary Efficacy Analysis

8.3.6.2.1 Duration of Morning Stiffness

As the duration of morning stiffness is expected not to be normally distributed, the difference between the treatment groups will be assessed using the median and the confidence interval of the median computed using Hodges Lehmann method (see appendix section 10.7).
The analysis will also be repeated for mean absolute and relative changes from baseline.
Duration of morning stiffness will be analyzed only on LOCF data and on the safety, mITT and PP populations.
In addition, the analysis will be presented for USA/Canada and for Europe in separate tables.

8.3.6.2.2 DAS28:

The relative change from baseline to visit 2, visit 3 and visit 4 for DAS28 will be analyzed using a mixed model with treatment, pooled sites as a nested effect of geographic region and the interaction between the nested effect and treatment. Pooled sites within geographic region will be defined as a random effect.
The following example of SAS code will be used:

proc mixed data= *dataset*;
class treat pooledsite region;
random pooledsite(region);
model change = base treat pooledsite(region)*treat/ solution;
lsmeans treat / pdiff CL;
run;

where: *treat:* treatment
pooledsite: pooled site
region: America or Europe
base: baseline score for each patient
change: relative change in score from baseline

The above mentioned model will also be repeated for mean absolute and relative changes from baseline. DAS28 will be analyzed on safety population and observed case as well as LOCF.

8.3.6.2.3 Time to response

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 Cox model stratified by geographic region. Time to first response is defined as the date when all the assessment leading to the ACR20 response has been collected.

The following example SAS code will be used:

```
proc lifetest data=dataset;
        time onset*censor(0);
        test treat;
run;
```

where: *treat*: treatment
onset: the time between baseline and a patient's first response to the ACR20 criteria
censor: censor flag

Hazard ratio using Cox model stratified by region will also be presented.

A SAS code similar to the following will be used.

```
proc phreg data=dataset;
        model onset*censor(0) = treat / risklimits;
        strata region;
        ods output parameterestimates=_paramsA;
run;
```

where: *treat*: treatment
onset: the time between baseline and a patient's first response to the ACR20 criteria
censor: censor flag
region: America or Europe

8.3.6.2.4 ACR50 and ACR70

ACR50 and ACR70 responder status at each visit endpoint will be tested separately using a logistic regression model with treatment as factor with a two-sided significance level of α=0.05 for the safety population. Observed data and LOCF imputation scheme will be analyzed.

Odds ratios for the difference between treatments and the associated 95% confidence interval, as well as the difference in proportion and its associated 95% confidence interval will be presented for each population.

A SAS code similar to the one below will be used for the primary endpoint analysis.

```
proc genmod data=dataset;
        class treat;
        model responder = treat / link=linkc dist=binomial type3;
        lsmeans treat / diff CL;
run;
```

where: *treat*: treatment
responder: responders those who met ACRX criteria (X = 50, 70)
non-responders those who did not meet ACRX criteria (X = 50, 70)
linkc: logit for the odds ratio estimation and identity for the confidence interval of the difference in proportion

8.3.6.2.5 EULAR Response:

EULAR response will be analyzed using logistic regression with treatment and geographic region as factors.

Odds ratios for the difference between treatments and the associated 95% confidence interval will be presented for the Safety population.

A similar code as the following will be used.

```
proc genmod data=dataset;
        class treat region;
        model responder = treat region / link= clogit dist=mult type3;
        lsmeans treat / diff CL;
run;
```

where: *treat*: treatment
region: America or Europe
responder: responders those who met ACR20 criteria
non-responders those who did not meet ACR 20 criteria

8.3.6.2.6 Usage of Additional Analgesics:

The number of days with additional analgesic use will be summarized and will be based on the number of days when additional analgesic were used over the treatment period (from first dose to last dose date). Wilcoxon rank sum test will be used to compare the number of days of analgesic use among treatment groups. P-value based on the normal approximation will be used.

The following example of SAS code will be used:

```
proc npar1way data=dataset WILCOXON;
        class treat;
        var analg;
run;
```

where: *treat*: treatment
analg: number of days additional analgesics used

8.3.6.2.7 Other parameters:

The following parameters will be analyzed using an ANCOVA.

- Tender joint count,
- Swollen joint count,
- Patient assessment of pain (VAS) - CRF data,
- Patient assessment of pain (VAS) morning and evening - diary data
- Patient's global assessment of disease activity (VAS),
- Physician global assessment of disease activity (VAS),
- Quality of life questionnaire: HAQ-DI, FACIT-Fatigue, FACIT-G and SF-36
- Inflammatory parameters: CRP, ESR, IL-6, TNFα
- Urine CTX
- Severity of morning stiffness
- Reoccurrence of morning stiffness
- Additional analgesics (proportion of days with use of analgesics within the last 7 days prior to visit)

FACIT-G questionnaire will only be summarized; no analysis of change from baseline will be analyzed.
The mean absolute change and relative change from baseline to endpoint will be analyzed using ANCOVA with treatment and geographic region as the factors.

If the change from baseline in CRP, IL-6 and TNFα, is not normally distributed (normality tested using Kolmogorov-Smirnov), the data will be log transformed before the analysis and then the estimates will be back transformed, in addition differences between the treatment groups will be assessed using the confidence interval and not the p-value (p-value corresponding to the log-transformed data).

The following example of SAS code will be used:

proc mixed data= *dataset*;
class treat region;
model change = base treat region / solution;
lsmeans treat / pdiff CL;
run;

where: *treat*: treatment
region: America or Europe
base: baseline score for each patient
change: absolute change in score from baseline

8.3.7 Safety Analysis

All summaries will be performed on the Safety population. All safety variables will be summarized by treatment groups using descriptive statistics. For categorical data, the number and percentage of patients will be presented and for continuous data the number of patients (n), mean, standard deviation (SD), median, minimum and maximum will be presented. Data will be summarized for baseline, endpoint and by visit.

8.3.7.1 Adverse Events

Absolute and relative frequencies of treatment emergent adverse events (TEAEs) will be calculated by system organ class and preferred term for all AEs, possibly related AEs, SAEs, and AEs leading to withdrawal.
All AEs count data will be summarized for the number of patients in each treatment group in whom the events occurred, and the rate of occurrence of the event. Incidence rates of TEAEs will be summarized by System Organ Class (SOC) and preferred term (PT) with respect to the Medical Dictionary for Regulatory Activities (MedDRA).

In addition, TEAEs will be summarized by seriousness, relationship to the study drug (‘Yes, reasonable causal relationship, ‘No causal relationship) for each treatment group.

If a patient has more than one occurrence of the same AE, the patient will be counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures, will be indicated in cases of multiple occurrences of the same AE.

AEs in the tables will be sorted by decreasing frequencies of SOC and PT. Supportive listings will be provided.

8.3.7.2 Laboratory Evaluation

The laboratory parameters include Hematology, Clinical Chemistry, and Urinalysis. Hematology and clinical chemistry will be analyzed for differential patterns of changes between treatment groups. Summary of laboratory results and shift table (between visit 4 and Baseline) will be presented.

Supportive individual listings will be provided.

8.3.7.3 Physical Examination

Physical Examination findings will be summarized by body system for each treatment group at Visit 0 and Visit 4. Shifts from normal to abnormal between baseline and endpoint will also be displayed.

Supportive individual listings will be provided.

8.3.7.4 Vital Signs

Vital signs (Blood pressure (mmHg) (systolic/diastolic), Pulse (beats/minute), Weight (kg) and Height (m)) will be summarized descriptively (value and absolute change from baseline) by visit (all visits) and treatment group.

8.3.7.5 Pregnancy Test

Findings from the HCG pregnancy test will only be listed.

9 REFERENCES

1. Guidelines for Industry: Structure and Content of Clinical Study Reports (E3), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, July 1996.

2. Guidelines for Industry: Statistical Principles for Clinical Trials (E9), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, September 1998.

3. Van Gestel AM, Anderson JJ, Van Riel PLCM et al.: ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. J Rheumatol 1999; 26: 705–711

10 APPENDIXES

The following section describes the table and listings templates, the algorithms, imputations and conventions that will generally apply to program derivations of the data as required to perform the proposed summary tabulations, individual patient data listings, and figures.

10.1 Tables template

See attached document (appendix II).

10.2 Listings template

See attached document (appendix III)

10.3 Layout

All computer-generated tables should be produces in landscape mode. The output area is restricted to 23.9 cm x 15.49 cm to allow printing both on letter and on A4 size paper with suitable margins. To achieve a readable output using SAS Monospace with font size 8 the following SAS option may not be exceed:

- Linesize=140
- Pagesize=46

The number of decimal places will be displayed as follows.

- Mean and median: one more than the number of decimal places allotted in the CRF.
- Standard deviation [SD]: two more than the number of decimal places allotted in the CRF.
- Minimum and maximum: equal to the number of decimal places allotted in the CRF.

Percentages will be presented with 1 decimal place.

The following number of decimal place for the derived variables will be used:

- Duration of RA will be presented with 1 decimal place.
- BMI will be presented with 1 decimal place.
- DAS28 will be presented with 1 decimal place.
- Diary data will be presented with 1 decimal place.
- HAQ-DI Score, 2 decimal places.
- SF-36 Scores, 1 decimal place.
- Fatigue Score and FACIT-G 1 decimal place.

10.4 Categorization

The following categorization will be used where applicable.

a. Age Classes

The patient will be summarized based on the following age categories.

- Young, if age is 45 years or less
- Middle-aged, if age is between > 45 and 65 years
- Elderly, if age is between > 65 and 75 years
- Very elderly, if age is > 75 years

b. Duration of Rheumatoid Arthritis

With regards to the duration of rheumatoid arthritis, the following categories are defined.

- < 2 years
- >= 2 to < 5 years
- >= 5 to < 10 years
- >= 10 years

c. Extent of Exposure

With regards to the total number of treatments days during the double blind treatment phase, the different categories are defined as follow.

- < 14 days
- >= 14 to < 28 days
- >= 28 to < 42 days
- >= 42 to < 56 days
- >= 56 to < 70 days
- >= 70 to < 84 days
- >= 84 days

d. Compliance with study medication

With regards to the percentage intake of study medication during the double blind treatment phase, the different categories are defined as follow.

- < 80%
- >= 80% to < 95%
- >= 85% to < 105%
- >= 105% to < 120%
- >= 120%

e. Disease Activity Score

With regards to the disease activity score, the different categories are defined as follow.

- Inactive, if DAS28 is 3.2 or less
- Moderate, if DAS28 is > 3.2 and =< 5.1
- Very Active, if DAS28 is > 5.1
- Not available if DAS28 is missing

10.5 Derivations

The following section provides details on the derivation of the variables used in the Tables, Listings and Figures.

a. Age

Age [years] is the integer of time from the date of birth [DOB] to date of informed consent [DOIC].

$$Age = INT(DOIC - DOB)$$

b. Duration of an event

Duration [days] is the difference between the end date [ENDT] and the start date [STDT] plus one day.

$$Duration = (ENDT – STDT) + 1$$

Conversion from days to years will be done by dividing the number of days by 365.25.

c. Duration of morning Stiffness

Daily Duration in morning stiffness [min] is the difference between the time of resolution of morning stiffness [ENTM] and the time of wake up [STTM] (both times expressed in minutes).

$$Duration\_Stiffness = (ENTM – STTM)$$

Due to missing or inconsistent subject diary entries (with regard to wake-up time, end of stiffness time, or stiffness yes/no marker) or due to entries which indicate that the morning stiffness on a particular day did not end, the above formula is not always applicable. The following table defines the rules to be applied depending on the relevant combination.

Wake-up time	End of morning stiffness	Stiffness (yes/no)	Calculated duration of stiffness
Missing	Missing or Documented	Missing or Documented	Missing
Documented	Missing	Missing	Missing
Documented	Missing	No	Set to 0
Documented before 12:00	Missing	Yes	12:00 – Wake up time
Documented after 12:00	Missing or Documented	Yes	Set to missing
Documented before 12:00	Documented before 12:00	Missing or No or Yes	End of stiffness – Wake up time
Documented before 12:00	Documented after 12:00 or reported as 00:00	Missing or No or Yes	12:00 – wake up time

If duration of stiffness is negative due to wrong entries of the wake up time or the time of end of stiffness, the duration will be set to missing. Different pages with the same date for the same patient will be analyzed as per section 10.6.
If the patient stated on the CRF diary that the morning stiffness did not subdue it was entered as 00:00 in the diary.

d. Duration, Age of onset of rheumatoid arthritis in case of partial date

If the date of diagnosis of rheumatoid arthritis is a partial date the following rules will be implemented to compute the duration of the rheumatoid arthritis and the onset age of rheumatoid arthritis.

Duration of RA:

- If the date of diagnosis is not missing or partial, then the duration of RA (in year) will be computed as: date of informed consent – date of diagnosis divided by 365.25.
- If only the year and month of diagnosis are recorded, the number of months between the date of informed consent and the date of diagnosis will be computed and converted to years by dividing by 30.4375.
- If only the year is recorded, the number of years between the two dates will be computed (for example, if both events occurred the same year, the duration of RA will be set to 0).

Onset Age of RA

- If the date of diagnosis is not missing or partial, then the onset age (year) will be computed as: integer of [(date of diagnosis – date of birth) divided by 365.25].
- If only the year and month of diagnosis are recorded, the number of months between the date of birth and the date of diagnosis will be computed and converted to years by taking the integer value of the number of months between the two events converted to years i.e. the integer value of the quotient of the difference in months and 30.4275.
- If only the year is recorded, the number of years between the two dates will be computed.

e. Prior/Concomitant medication and TEAEs partial date

Treatment emergent Adverse Events:

- If the start date is not partial and is on or after the first dose of medication then the AE is a treatment emergent adverse event.
- If the start date of the AE is a partial date, the AE will be classified as TEAE only in the following scenario:
  - if the year of the start of the AE event is after the year of the first dose
  - if the year is the same for both the first dose and the start of the AE and the month of the AE start date is on or after the month of the first dose or if the month is missing
  - if the AE start date is missing

Concomitant medications:

- If the start date is not partial and is on or after the first dose of medication then the medication is concomitant.
- If the start date of the medication is a partial date, the medication will be classified as concomitant only in the following scenario:
  - if the year of the start date of the medication is after the year of the first dose
  - if the year is the same for both the first dose and the start of the medication and the month of the medication start date is on or after the month of the first dose or if the month is missing
  - if the medication start date is missing and the medication is ongoing

Prior medications:

- If the start date is not partial and is strictly before the first dose of medication then the medication is a prior medication.
- If the start date of the medication is a partial date, the medication will be classified as prior only in the following scenario:
  - if the year of the start date of the medication is before the year of the first dose
  - if the year is the same for both the first dose and the start of the medication and the month of the medication start date is on or before the month of the first dose or if the month is missing

f. HAQ-DI Score

The subject must have a score for at least 6 of the 8 categories. If there are less than 6 categories completed, the HAQ-DI score cannot be computed.

- The highest score reported for any component question of the eight categories determines the score for that category
- If either devices and/or help from another person are checked for a category and the highest score for this category is 0 or 1 then the score is set to 2. The other categories will be ignored.
- A global score is calculated by summing the scores for each of the categories and dividing by the number of categories answered

The aids or devices and help from another person are linked to the 8 categories as follows.

Category	Aids or devices	Help from another person
Hygiene	Raised toilet seat Bathtub seat Bathtub bar Long-handled appliances in bathroom	Hygiene
Reach	Long-handled appliances for reach	Reach
Grip	Jar opener (for jars previously opened)	Gripping and opening things
Activities		Errands and chores
Dressing and grooming	Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)	Dressing an d grooming
Arising	Special or built up chair	Arising
Eating	Built up or special utensils	Eating
Walking	Cane Walker Crutches	Walking

g. SF-36 Score

The SF-36v2 scoring system requires 2 assumptions: (i) a higher score indicates a better health state and (ii) there is a linear relationship between the item scores and the underlying health concepts defined by their scales. As not all the raw item scores recorded for the SF-36v2 satisfy these assumptions, some recoding is required. All questions will be scored as per the raw data values collected on the eCRF with the following exceptions:

- Seven questions will have their coding inversed so that 5=1, 4=2, 3=3, 2=4 and 1=5. These questions are: 6, 9a, 9d, 9e, 9h, 11b and 11d.

The SF-36v2 scoring system relies on an assumption of linearity among the responses. However, for 3 of the 36 questions, it was found that the intervals were not evenly spaced among some of the qualitative responses so the values were recoded to preserve the linearity assumption. The questions affected are question 1 (General Health) and questions 7 and 8 (Bodily Pain).

Question 1 (General Health)

Q1 (verbatim responses)	Q1 (raw value)	Q1 (recoded)
Excellent	1	5.0
Very good	2	4.4
Good	3	3.4
Fair	4	2.0
Poor	5	1.0

Question 7 (Bodily Pain)

Q7 (verbatim responses)	Q7 (raw value)	Q7 (recoded)
None	1	6.0
Very mild	2	5.4
Mild	3	4.2
Moderate	4	3.1
Severe	5	2.2
Very severe	6	1.0

Question 8 will have its score inversed too, but also depends on the response given for question 7, in the following manner:

Q7 (raw value)	Q8 (verbatim responses)	Q8 (raw value)	Q8 (recoded)
1	Not at all	1	6
2, 3, 4, 5 or 6	Not at all	1	5
any	A little bit	2	4
any	Moderately	3	3
any	Quite a bit	4	2
any	Extremely	5	1

If question 7 is not answered then question 8 will have its score recoded to preserve linearity, in the following manner:

Q7 (raw value)	Q8 (verbatim responses)	Q8 (raw value)	Q8 (recoded)
missing	Not at all	1	6.0
missing	A little bit	2	4.75
missing	Moderately	3	3.5
missing	Quite a bit	4	2.25
missing	Extremely	5	1.0

Domain Scores

The 8 health domains are comprised of the individual items as follows:

- Physical Functioning Score => (Q3A Q3B Q3C Q3D Q3E Q3F Q3G Q3H Q3I Q3J)
- Role-Physical Score => (Q4A Q4B Q4C Q4D)
- Bodily Pain => (Q7 Q8)
- General Health Score => (Q1 Q11A Q11B Q11C Q11D)
- Vitality Score => (Q9A Q9E Q9G Q9I)
- Social Functioning Score => (Q6 Q10)
- Role-Emotional Score => (Q5A Q5B Q5C)
- Mental Health Score => (Q9B Q9C Q9D Q9F Q9H)

Note that Q2 is a general question and is not contained in any of the scales.

The answers to each question (recoded as necessary) are summed for each subject at each visit, within each of the 8 domains. If an item is missing, it should be imputed as the mean of the non-missing items in its domain for the purposes of calculating the domain score. Note that this imputation applies only to the calculation of the domain scores; imputation of individual item scores will not be presented. At least 50% of the item scores in a domain must be non-missing to calculate the domain score, otherwise the domain score is set to missing.

The resulting score for each domain (after the imputation described above) is then standardised, to obtain values ranging from 0 to 100, with higher values indicating a better quality of life.

$$\text{Standardised Score} = \left[\left(\frac{\text{sum} - \text{lowest possible score}}{\text{possible raw score range}} \right) \right] \times 100$$

- Physical and Mental Component Summary Scale.

Physical and Mental Summary Scale are computed based on the US based population standardization. The scoring of these two component summary scale involved the three following steps:

- Standardization of the 8 domains of the SF-36 as computed previously, as per following formula.
  - PFZ = (Physical Functioning Score - 84.52404) / 22.89490
  - RPZ = (Role-Physical Score - 81.19907) / 33.79729
  - BPZ = (Bodily Pain Score - 75.49196) / 23.55879
  - GHZ = (General Health Score – 72.21316) / 20.16964
  - VTZ = (Vitality Score – 61.05453) / 20.86942
  - SFZ = (Social Functioning Score – 83.59753) / 22.37642
  - REZ = (Role-Emotional Score – 81.29467) / 33.02717
  - MHZ = (Mental Health Score – 74.84212) / 18.01189
- Weighting and aggregation of the 8 domains scores
  - AGG_PHYS = 0.42402×PFZ + 0.35119×RPZ + 0.31754×BPZ + 0.24954×GHZ + 0.02877×VTZ – 0.00753×SFZ - 0.19206×REZ - 0.22069×MHZ
  - AGG_MENT = -0.22999×PFZ – 0.12329×RPZ - 0.09731×BPZ - 0.01571×GHZ + 0.23534×VTZ+ 0.26876×SFZ + 0.43407×REZ + 0.48581×MHZ
- Transforming the aggregate scale score to a T-score
  - Physical Component Score = 50 + 10×AGG_PHYS
  - Mental Component Score = 50 + 10×AGG_MENT

h. FACIT-F and its subscales scores

The following derivation will be performed on the items and subscale scores in order to compute the FACIT-F Score.

Subscale	Items	Score
Physical Well-being (PWB)	All items	4 – raw score
Social/family Well-Being (SWB)	All items	Raw score
Emotional Well-Being (EWB)	Q1 and Q3 to Q6	4 – raw score
Emotional Well-Being (EWB)	Q2 (I am satisfied with how I am coping with my illness)	Raw score
Functional Well-Being (FWB)	All items	Raw Score
Fatigue Subscale (FS)	Q1 to Q6 and Q9 to Q13	4 – raw score
Fatigue Subscale (FS)	Q7 (I have energy)	Raw Score
Fatigue Subscale (FS)	Q8 (I am able to do my usual activities)	Raw Score

Subscale score is computed as follow:

$$\text{Subscale Score} = \frac{\text{Sum of the Item} \times \text{Number of items}}{\text{Number of items answered}}$$

Subscale	Number of items
Physical Well-being (PWB)	7
Social/family Well-Being (SWB)	7
Emotional Well-Being (EWB)	6
Functional Well-Being (FWB)	7
Fatigue Subscale (FS)	13

Total Score of FACIT-F is the sum of the subscale scores. Total score ranges from 0 to 160.
Total Score of FACIT-G is the sum of the subscale scores (PB, SWB, EWB and FWB). Total score ranges from 0 to 108.

If more than 50% of the items (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc) within a subscale are missing the subscale score cannot be computed. The FACIT scale is considered to be an acceptable indicator of patient quality of life as long as overall item response rate is greater than 80% (e.g., at least 32 of 40 FACT-F items completed, 22 of 27 for the FACT-G). If the total number of items answered is less than 80% the FACIT-F and FACIT-G score cannot be computed and will be set to missing.

10.6 Collapsing the diary information

Twice daily the patients were asked to fill the diary (one page for the morning and one page for the afternoon). At each visit a new diary was provided to the patient and the completed one was retrieved by the investigator during the visit. On the day of the visit the afternoon diary page was not completed by the patient as it was kept with the investigator. The afternoon data of the visit day is recorded on the diary using different methods.

- Scenario 1: the afternoon page was removed from the diary during the visit and stapled to the new diary.
- Scenario 2: the afternoon was completed on the afternoon of the day 1 of the new diary
- Scenario 3: the afternoon was completed on the afternoon of one of the additional pages
- Scenario 4: the afternoon was completed on the afternoon of one of the additional pages and the morning was recopied from the morning data.

However, as the date corresponding to the diary information is recorded only on the morning page, in order to link morning and afternoon data across the same visit the following rules have been applied to the programming of the diary data.

If two pages have the same date but the data were reported on consecutive visits, the two dates will be collapsed using the worse case scenario (see below).
If the first page (day 1) on the next diary has a missing date and the following day entry correspond to the day after the visit, then day 1 will be linked to the last day of the previous diary.
If the afternoon page (scenario 3) has a day out of sequence, the afternoon page will be linked to the last day of the previous visit.
If the morning and afternoon pages (scenario 4) has a day out of sequence, the morning and afternoon pages will be linked to the last day of the previous visit.

If for a diary visit a patient provided only one page with an afternoon data (whatever the day entered), it will be associated with the last day of the previous visit.

In order to implement the above rules, the page number, date and day of the diary were used to impute missing information and be able to collapse the data.
It is expected that it will not always be possible to link morning and afternoon data for the following reasons:

- missing date and day on the diary
- wrong day entered

Therefore these pages, for which it is not possible to associate a date, will be removed from the diary data and not listed.

It is assumed that day 0 entries corresponds to the day of the visit n the date of the diary entry will be imputed using that assumption.

In addition, it is also expected that some of pages of the diary will not be recorded with the correct date. If it is not possible to self evidently correct the date (done by data management), the diary information were collapsed with the other entries recorded on the same date by using the worse case scenario.

Worse case is defined as follows. If one or more values for the same date is missing then the missing will be disregarded, if all values are missing then the variable will be set to missing.

- Time of wake up: minimum of the different times available for the same date
- Presence of stiffness at wake up: set to yes if at least one of the values is set to yes for the same date, set to the no or missing otherwise
- Severity of morning stiffness: maximum of the different values of the VAS for the same date
- Time of morning stiffness subdue: maximum of the different times available for the same date
- Intensity of pain at wake up: maximum of the different values of the VAS for the same date
- Time of medication intake: the time which represents the greatest deviation from 22:00 then the latest.

- Reoccurrence of pain: set to yes if at least one of the values is set to yes for the same date, set to the no or missing otherwise
- Intensity of pain during the day:
- Additional painkiller taken: set to yes if at least one of the values is set to yes for the same date, set to the no or missing otherwise. If painkiller information has been recorded on the same page set to yes.
- Painkiller dose/time information: take all medications recorded on the different pages.

10.7 Hodges-Lehmann Estimate of Between Treatment Difference in Medians

Step 1: Create 2 separate datasets, one for each treatment group, and create a separate variable for the response.
Step 2: Calculate all possible differences between the 2 treatment groups.
Step 3: Calculate the median of these differences

Corresponding distribution-free CI (based on the Wilcoxon Rank Sum test) to be calculated as follows:

Lower limit: $0^{C\alpha}$
Upper limit: $0^{(XY+1-C\alpha)}$

where:

X = sample size for first treatment group
Y = sample size for second treatment group
C_α is an integer that approximates the ordered value of the lower confidence interval

For large samples C_α is an integer approximated by the following:

$C_\alpha \approx XY/2 - Z_{\alpha/2} [XY(X+Y+1)/12]^{1/2}$

Note: $\alpha = 0.05$ for the calculation of a 95% CI

Low-dose prednisone chronotherapy for rheumatoid arthritis: A randomised clinical trial (CAPRA-2)

SUPPLEMENTARY MATERIAL

Inclusion and Exclusion criteria

Key inclusion criteria for the study were: diagnosis of RA; documented history of RA (sero-negative or sero-positive) in agreement with American College of Rheumatology (ACR) criteria, including having symptoms of morning stiffness, joint pain, tender and swollen joints, and an inflammatory state with elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); treatment with DMARDs for RA for at least 6 months, with a stable dose for at least 6 weeks before the screening visit; duration of morning stiffness of at least 45 minutes on at least 4 days within the 7 days of screening; having a swollen joint count at least 4 out of 28 and a tender joint count of at least 4 out of 28; and age 18–80 years. In addition, female patients of childbearing potential had to be using a medically accepted contraceptive regimen.

Key exclusion criteria were: having another condition that required glucocorticoid treatment during the study period; synovectomy within 4 months before the study start; use of glucocorticoids; continued use of systemic glucocorticoids within 4 weeks before the screening visit; intermittent use of glucocorticoids (defined as a maximum of 7 days' treatment with a cumulative dose of ≤100 mg prednisone or equivalent in the 6 weeks before the screening visit) within 2 weeks before the screening visit; intra-articular glucocorticoid injections in the 6 weeks before the

screening visit; use of biological therapies such as TNFα inhibitors within 5 serum half-lives before the screening visit; clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation; pregnancy or nursing; alcohol or drug abuse; significant renal impairment (serum creatinine >150 µmol/L); significant hepatic impairment (as judged by the investigator).

Randomisation

Patients were assigned to treatment by giving a unique 4-digit patient number to each patient who had provided informed consent. The randomisation schedule was generated by the Contract Research Organization and linked sequential numbers to treatment codes allocated at random with a 2:1 (MR prednisone vs placebo) randomisation ratio. The randomisation numbers were blocked: within each block, patients were allocated to each of the two treatment groups. The block size was not revealed. Randomisation to study medication was balanced by investigational site. The investigational product was labelled with a three-digit randomisation number. The next patient eligible for randomisation was to receive the lowest available medication number within the study site. The investigator documented the medication number in the case report form. The randomisation schedule was kept by the randomisation code administrator who was independent of the study team. A copy of the randomisation schedule was provided to the drug supplier responsible for packaging the investigational products. Tablets were taken with or after the evening meal, at about 10:00 p.m. Both tablets were identical in appearance, and patients and investigators were blinded to treatment.

Permitted and prohibited concomitant medications

In the event of an acute exacerbation of pain, patients were permitted to take a non-anti-inflammatory pain-killing drug, preferably paracetamol, and this was to be recorded in the patient's diary. The following concomitant treatments were not permitted during the study: glucocorticoids other than the study medication, intra-articular injections, synoviorthesis, biological therapies, and initiation of DMARD or non-steroidal anti-inflammatory drug (NSAID) therapy.

Secondary endpoints

In addition to the key secondary endpoint, duration of morning stiffness, the following secondary efficacy endpoints are reported in this paper: proportions of patients with a 50% or a 70% improvement in RA signs and symptoms according to ACR criteria (i.e. ACR50 and ACR70 responses, respectively), change from baseline in the individual ACR core set measures, and change from baseline in: severity of morning stiffness, recurrence of stiffness during the day, morning and evening pain, inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] measured at each study visit and IL-6 and TNFα measured at screening and week 12), and measures of health-related quality of life. Routine clinical laboratory assessments were conducted at baseline and week 12. The following additional secondary endpoints were assessed during the study but are not reported here: time to ACR20 response, response according to the European League Against Rheumatism criteria, change from baseline in urine C-terminal cross-linked telopeptides of collagen type I, and analgesic use.

Calculation of duration of morning stiffness

Duration of morning stiffness was the difference between the time of resolution of morning stiffness and the time of waking. The latest resolution time for morning stiffness was set to noon; therefore, if the time when the morning stiffness eased was after noon, this was censored at noon, and duration of morning stiffness was noon minus the time of getting up in the morning. Duration of morning stiffness was calculated as the average of the morning stiffness duration in the 7 days before the visit (including the day of the visit). If more than four assessments were missing, the duration was set to missing. If at least four assessments were available, the 7-day average was calculated using the available values from the 7 days before the visit day for the duration of morning stiffness (LOCF).

Statistical analyses

The primary analysis of the study was according to treatment received, as specified in the statistical analysis plan. Data were analysed both according to treatment received and according to treatment assigned (intention-to-treat, ITT). Where comparison to baseline was required, data were analysed for the modified ITT (mITT) group which excluded patients without baseline data. All analyses yielded consistent results. Results of the ITT (of mITT where appropriate) analysis are reported here. Safety data were analysed according to received treatment. The last-observation-carried-forward (LOCF) method was used for patients who discontinued study treatment prematurely.

A logistic regression model with treatment as a factor was used to assess ACR50 and ACR70 response rates using a two-sided significance level of $\alpha = 0.05$. Relative

changes from baseline for all ACR core set measures except DAS28, other clinical measures (morning pain score, evening pain score, severity of morning stiffness and recurrence of stiffness) and health-related quality of life measures (FACIT-F score, SF-36 physical component score and SF-36 mental component score) were analysed using analysis of covariance (ANCOVA) with treatment and geographical region as factors. Relative change from baseline for DAS28 was analysed using a mixed model with treatment, pooled sites as a nested effect of geographical region, and the interaction between the nested effect and treatment. For assessment of the change from baseline in the inflammatory markers, CRP, IL-6 and TNFα, data were log transformed before the analysis and the estimates were back transformed as these were not normally distributed. Differences between treatment groups for these inflammatory markers were assessed using the 95% CI.

Supplementary Table 1. Patient locations.

Principal investigator	Town/City	Number of patients
USA		
Mehta	Elizabethtown	13
Huh	Los Angeles	2
Kempf	San Antonio	2
Codding	Oklahoma City	4
Cruse	Tampa	4
Kades	Los Angeles	3
Dikranian	San Diego	1
Huff	San Antonio	5
Kennedy	Vero Beach	2
Kirby	Belmont	5
Lee	Upland	6
Rapoport	Fall River	3
Raskin	Pacific Palisades	1
Fairfax	Mesa	3

Principal investigator	Town/City	Number of patients
Trapp	Springfield	4
Archuleta	Wheat Ridge	3
DeGarmao	Greer	2
Hagan	Billings	2
Khan	Bellevue	1
Kimmel	Tamarac	1
Bode	Tucson	4
Goldberger	Perrysburg	1
Lowenstein	Palm Harbour	3
		Total = 75
Canada		
Rodriguez	Windsor	11
Lee	Pickering	2
		Total = 13
Germany		
Buttgereit	Berlin	1
Alten	Berlin	1

Principal investigator	Town/City	Number of patients
Krüger	München	1
		Total = 3
Hungary		
Gal	Kecskemét	7
Náfrádi	Szombathely	6
Nékám	Budapest	6
Sámson	Szolnok	6
Surányi	Debrecen	12
Szántó	Debrecen	18
Takács	Kiskunhalas	12
Balázs	Bekescsaba	5
Szombati	Budapest	30
		Total = 102
Poland		
Szechinski	Wroclaw	27
Dudek	Warszawa	13
Jeka	Torun	19

Principal investigator	Town/City	Number of patients
Mackiewicz	Poznan	7
Majdan	Lublin	4
Sierakowski	Bialystok	16
Sochoka-Bykowska	Sopot	4
Supronik	Bialystok	30
Brzezicki	Elblag	24
Ruzga	Wroclaw	1
		Total = 145
UK		
Kirwan	Bristol	2
George	Upton	1
Szbenyi	Grimsby	9
		Total = 12

Supplementary Table 2. Concomitant DMARD and NSAID therapy at baseline and the end of the study taken by more than 2% of patients.

	Baseline			End of Study		
Concomitant medication, % (n)	MR Prednisone (N=231)	Placebo (N=119)	Total (N=350)	MR Prednisone (N=231)	Placebo (N=119)	Total (N=350)
DMARDs						
Any DMARDs medication	97.0 (224)	96.6 (115)	96.9 (339)	98.3 (227)	100.0 (119)	98.9 (346)
Methotrexate*	74.5 (172)	65.5 (78)	71.4 (250)	74.5 (172)	68.1 (81)	72.3 (253)
Sulfasalazine	15.6 (36)	12.6 (15)	14.6 (51)	15.6 (36)	12.6 (15)	14.6 (51)
Leflunomide	9.5 (22)	13.4 (16)	10.9 (38)	9.5 (22)	13.4 (16)	10.9 (38)
Hydroxychloroquine*	8.2 (19)	10.1 (12)	8.9 (31)	7.8 (18)	10.1 (12)	8.6 (30)
Analgesics						
Any concomitant analgesics medication	83.5 (193)	86.6 (103)	84.6 (296)	77.9 (180)	81.5 (97)	79.1 (277)

*A small number of patients underwent changes in DMARD therapy during the study despite this being prohibited by study protocol; however these were not uncovered until unblinding.

Supplementary Table 3. Patients achieving low disease activity/remission.

Proportion of patients achieving disease status, % (n)	**MR prednisone N = 231**	**Placebo N = 119**	**p-value**
At 2 weeks			
Low disease activity	6.5 (15)	5.9 (7)	1.0000
Remission of disease	3.0 (7)	1.7 (2)	0.7237
At 6 weeks			
Low disease activity	19.1 (44)	5.9 (7)	0.0007
Remission of disease	8.7 (20)	2.5 (3)	0.0381
At 12 weeks			
Low disease activity	27.4 (63)	15.1 (18)	0.0109
Remission of disease	11.3 (26)	6.7 (8)	0.1882

Remission of disease was defined as a 28-joint disease activity (DAS28) score < 2.6.

Low disease activity was defined as a DAS28 score < 3.2.

p-value calculated with Fisher's exact test.

Supplementary Table 4. Duration of morning stiffness relative to disease duration.

Change in morning stiffness from baseline at week 12, Median (95% CI)	**MR prednisone N = 231**	**Placebo N = 119**
< 2 years RA		
Number of patients	38	26
Duration (minutes)	-51.8 (-80.7 to -27.7)	-28.7 (-53.6 to 38.6)
Percentage change	-48.1 (-73.7 to -10.8)	-19.3 (-43.9 to 17.0)
≥ 2 years to < 5 years		
Number of patients	58	23
Duration (minutes)	-62.1 (-88.7 to -38.6)	-30.0 (-89.1 to 2.9)
Percentage change	-69.8 (-83.6 to -36.1)	-33.3 (-58.1 to 2.1)
≥ 5 years to < 10 years		
Number of patients	52	25
Duration (minutes)	-56.9 (-90.0 to -47.1)	-32.1 (-70.7 to -7.5)
Percentage change	-63.8 (-81.7 to -42.0)	-37.8 (-70.5 to -11.1)
≥ 10 years		
Number of patients	68	33
Duration (minutes)	-54.4 (-66.0 to -28.1)	-50.7 (-91.0 to -22.3)

Change in morning stiffness from baseline at week 12, Median (95% CI)	**MR prednisone N = 231**	**Placebo N = 119**
Percentage change	-54.9 (-82.1 to -34.0)	-42.1 (-72.1 to -21.1)

Patient numbers do not add up to total N value for each group as this analysis uses last observation carried forward and post-baseline data was not collected from all patients.

RA, rheumatoid arthritis; CI, confidence interval.

Supplemental Table 5. Integrated safety analysis for the first 3 months of treatment with prednisone.

Preferred Term	MR prednisone (N=375)	IR prednisone (N=144)	Placebo (N=119)
SAE (any event)	1.3%	2.1%	1.7%
Any Event			
Mild	18.4%	17.4%	29.4%
Moderate	21.1%	19.4%	15.1%
Severe	2.4%	2.8%	4.2%
AEs reported in > 2% of patients			
Aggravated RA/RA flare-up	12.8%	9.7%	26.1%
Nasopharyngitis	4.3%	5.6%	3.4%
Headache	4.0%	3.5%	4.2%
Nausea	2.1%	2.8%	0%
Abdominal pain upper	1.6%	5.6%	1.7%
Bronchitis	1.3%	3.5%	4.2%
Vertigo	1.1%	3.5%	0%
Diarrhoea	1.1%	2.8%	0.8%

Preferred Term	MR prednisone (N=375)	IR prednisone (N=144)	Placebo (N=119)
Dyspepsia	0.8%	2.1%	0%
Upper respiratory tract infection	0.5%	2.1%	0.8%
Chest pain	0.5%	2.1%	0%

Integrated safety analysis for patients receiving treatment with: 1) MR prednisone for 3 months in CAPRA-1 (n = 144) or CAPRA-2 (n = 231); IR prednisone for 3 months in CAPRA-1 (n = 144); or placebo for 3 months in CAPRA-2 (n = 119).

There were ten SAEs and one death (in the IR prednisone group) during the first 3 months of the integrated safety analysis; none were considered by the investigator to be related to study medication. SAEs recorded were tendon rupture, thumb osteoarthritis, spinaliom right cheek, Baker's cyst, myocardial infarction, disorder of consciousness, chest pain, abdominal pain exacerbation, palpitations, ischemic heart disease and abnormal cytology.

SAE, serious adverse event; MR, modified release; IR, immediate release; RA, rheumatoid arthritis; CAPRA, Circadian Administration of Prednisone in Rheumatoid Arthritis.

Safety data for CAPRA-1 have been presented previously.[1]

Supplemental Table 6. Integrated safety analysis for 12 months treatment with prednisone.

Preferred Term	MR prednisone months 1–12 (N=120)	IR prednisone months 1–3, MR prednisone months 4–12 (N=129)	All patients (N=249)
SAE (any event)	12.5%	14.7%	13.7%
Any Event			
Mild	18.3%	7.8%	12.9%
Moderate	27.5%	36.4%	32.1%
Severe	3.3%	7.0%	5.2%
AEs reported in > 2% of patients			
Aggravated RA/RA flare-up	14.2%	16.3%	15.3%
Flushing	4.2%	9.3%	6.8%
Back Pain	3.3%	2.3%	2.8%
Upper respiratory tract infection	3.3%	2.3%	2.8%

Preferred Term	MR prednisone months 1–12 (N=120)	IR prednisone months 1–3, MR prednisone months 4–12 (N=129)	All patients (N=249)
Weight increase	3.3%	2.3%	2.8%
Feeling hot	1.7%	3.9%	2.8%
Osteoarthritis	1.7%	3.1%	2.4%
Tachycardia	0.8%	2.3%	1.6%
Synovectomy	0%	2.3%	1.2%

Patients received the first 3 months treatment with either MR prednisone or IR prednisone. All patients then received a further 9 months treatment with MR prednisone. Data reported are overall safety data from months 0–12 of study.

Weight increase was self-reported by the patient.

There were 51 SAEs in 33 subjects. Of these only two were considered by the investigator as possibly related to treatment; perforation of stomach ulcer and digestive system bleeding; both occurred in the MR prednisone group. No deaths were reported.

SAE, serious adverse event; MR, modified release; IR, immediate release; RA, rheumatoid arthritis.

Safety data for the CAPRA-1 extension study have been presented previously.[2]

References

1 Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet*. 2008;**371**(9608):205-14.
2 Buttgereit F, Doering G, Schaeffler A, et al. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann Rheum Dis*. 2010;**69**(7):1275-80.