CLINICAL STUDY PROTOCOL

A Phase III, Randomized, Double-Blind, Double Dummy, Active Controlled, Multi-Center Study To Evaluate The Efficacy And Safety Of Intravenous Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) Compared With Intramuscular Injection Of Methylprednisolone Acetate In Subjects With Active Rheumatoid Arthritis

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PROTOCOL TITLE

A Phase III, Randomized, Double-Blind, Double Dummy, Active Controlled, Multi-Center Study To Evaluate The Efficacy And Safety Of Intravenous Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) Compared With Intramuscular Injection Of Methylprednisolone Acetate In Subjects With Active Rheumatoid Arthritis

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Coordinating Investigator	[redacted]
Medical Monitor	[redacted]
Clinical Research Organisation:	[redacted]
Sponsor	Vishwanath Kenkare Manager Business Development Sun Pharma Global FZE Office No. 43, Block-Y, SAIF Zone P.O. Box No. 122304 Sharjah, United Arab Emirates Ph: 00 971 4 454 8627 Fax: 00 971 4 454 8465 Email: vishwanath.kenkare@sunpharma.com

Sponsor's Clinical representative	Shantanu Mehta MD Deputy General Manager- Clinical Research Sun Pharma Advanced Research Company Ltd, 17-B, Mahal Industrial Estate, Mahakali Caves Road, Andheri (E) Mumbai, India - 400 093 e-mail: shantanu.mehta@sparcmail.com T: + 9122 66455645 ext 5635
Quality Assurance	[redacted]
Laboratory sites (central/local laboratory, pharmacokinetics analytical facility), Data management/statistical facility	Will be documented separately

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Sponsor: Vishwanath Kenkare		
Medical Monitor: Cornelis Wortel, MD, PhD		
Sponsor's Clinical Representative: Shantanu Mehta MD		
Coordinating Investigator: Prof. Dr. J.W.J. Bijlsma		
Biostatistician: Erich Geschwentner		
Medical Writer: Leonie Middelink		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood Urea Nitrogen
CA	Competent Authority
CK	Creatine kinase
Ca^{++}	Calcium
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRP	C-reactive protein
DAS28	Disease Activity Score in 28 Joints
DMARDs	Disease-modifying antirheumatic drugs
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e.g.	*exempli gratia* (for example)
EMA	European Medicines Agency
EOS	End of study
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EudraCT	European drug regulatory affairs Clinical Trials
FACIT	The Functional Assessment of Chronic Illness Therapy
GC	Glucocorticoid
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
HAQ	Health Assessment Questionnaire
HbA1c	Hemoglobin A1c
HCT	Hematocrit
HCV	Hepatitis C virus
HDL	High-density lipoprotein
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IA	Intra-articular
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International conference on harmonization

i.e.	*id est* (that is)
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent To Treat
IV	Intravenous
IWRS	Interactive Web-based Randomization System
K^+	Potassium
Kg	Kilogram(s)
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MCTD	Mixed Connective Tissue Disease
Mg	Milligram(s)
Min	Minute(s)
mL	Milliliter(s)
MM	Medical Monitor
MTX	Methotrexate
MS	Multiple sclerosis
Na^+	Sodium
NSAIDs	Non-steroidal anti-inflammatory drugs
PE	Physical examination
PEG	Polyethylene glycol
PI	Principal Investigator
PK	Pharmacokinetic(s)
PLP	Prednisolone sodium phosphate
PP	Per protocol
PRO	Patient Reported Outcome
PV	Pharmacovigilance
QA	Quality Assurance
QoL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red blood cells
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical analysis plan
SD	Standard deviation
SF-36	Short Form 36
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLE	Systemic lupus erythematosus
SPC	Summary of Product Characteristics

SUSAR	Suspected Unexpected Serious Adverse Reaction
VAS	Visual Analogue Scale
WBC	White blood cells

SUMMARY

Rationale:

Inflammatory disorders, such as rheumatoid arthritis (RA), are chronic, progressive, and debilitating diseases that often lead to disability. Adequate treatment is difficult and costly, and hospitalization often occurs [1]. Prednisolone and some other glucocorticoids (GCs) can be highly effective in treating joint inflammation, but their systemic application is limited because of a high incidence of serious adverse effects, especially related to long-term treatment [2, 3]. Besides a poor safety profile, also poor localization in inflamed areas in the body limits the usefulness of glucocorticoids in the patient [4]. Prednisolone sodium phosphate (PLP) encapsulated in long-circulating liposomes (Nanocort®) is being developed with the prospect of providing enhanced localized exposure over existing systemic formulations of glucocorticoids in certain "flare-ups" of inflammatory diseases that currently benefit from prednisolone administrations. As a result, Nanocort might be able to significantly reduce frequency of administration and use of the glucocorticoids compared to the treatment with intramuscular (IM) corticosteroids and so has a safety advantage.

This study is designed to evaluate the safety and efficacy of intravenous (IV) polyethylene-glycosylated (PEG)-liposomal prednisolone sodium phosphate (Nanocort) in RA subjects with flare/exacerbation.

Objective:

Primary objective: To assess efficacy and safety (treatment of signs and symptoms) of Nanocort in subjects with active rheumatoid arthritis who are experiencing a flare/exacerbation in comparison to a standard of care medication (Depo-Medrol).

Secondary objectives: Patient Reported Outcomes and an assessment of pharmacokinetic parameters in a subset population from each treatment group.

Study design:

The study is a randomized, double- blind, double dummy, active controlled, parallel, multi-center study in which IV Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) will be compared with IM injection of methylprednisolone acetate (Depo-Medrol®) to evaluate efficacy and safety. Each patient will receive an infusion and an IM injection containing either an active treatment or a dummy treatment. Opaque IV lines, sleeved bags and opaque syringes will be used to maintain blinding of either liposomal product or reference product.

All subjects will be provided an informed consent form (ICF) containing information about the study. After fully understanding of the ICF, subjects will voluntarily sign the ICF. Subjects will enter a screening period for up to 14 Days to assess laboratory values and other inclusion/exclusion criteria. Medical history and serious medical conditions as determined by the Principal Investigator (PI) will be reviewed during screening. In addition, the screening period will include a physical examination, blood and urine collection for laboratory assessments, vital signs, electrocardiogram (ECG) and confirmation of RA diagnosis (flare criteria).

Subjects with active RA who meet all eligibility criteria will undergo Baseline visit (Day 1) assessments. At this visit, prior to receiving treatments, subjects will be assessed for baseline parameters and then will be randomized into one of three groups:

- **Nanocort 75 mg** IV infusion and IM saline injection on Day 1 and Day 15
- **Nanocort 150 mg** IV infusion and IM saline injection on Day 1 and Day 15
- **Depo-Medrol®** 120 mg IM injection and IV saline infusion on Day 1 and Day 15

Dosing will occur on Baseline (Day 1) and Week 2 (Day 15). Study visits will occur at Week 1, Week 2, Week 3, Week 4, Week 6, Week 8 and Week 12 / End of Study (EOS) to assess efficacy and safety evaluations as indicated in the Schedule of Assessments. Subjects receiving any treatment dose will be followed till Week 12 for safety if possible.

Study population:

Male and female subjects (≥ 18 years) with diagnosed active RA who are experiencing a flare / exacerbation defined as recently switched from a period with -well documented- remission or low disease activity to an active disease (DAS28 ≥ 3.2). This documentation is either based on available detailed DAS28 values (increase in DAS28 > 1.2 or > 0.6 if DAS28 ≥ 3.2 compared to last DAS28 measurement (maximum 06 months before screening), or on a clear description of the previous low disease state by the treating physician (maximum 06 months before screening). The increase in disease activity has to be RA related.

Intervention:

A total of up to 330 subjects will be enrolled and randomized into 3 groups indicated below:

- **Nanocort 75 mg** IV infusion and IM saline injection (110 subjects)
- **Nanocort 150 mg** IV infusion and IM saline injection (110 subjects)
- **Depo-Medrol®** 120 mg IM injection and IV saline infusion (110 subjects)

Subjects in this trial will be randomized to receive an IM injection of 120 mg methylprednisolone acetate (Depo-Medrol®) or 75 mg/infusion of Nanocort administered as

an IV infusion or 150 mg/infusion of Nanocort administered as an IV infusion, on Day 1 and 15.

Study endpoints/parameters:

Primary Endpoint: European League Against Rheumatism (EULAR) responder (moderate and good combined) rate at Week 1 (Day 8)

Key Secondary Endpoints:

- EULAR responder (only good) rate at Week 1 (Day 8)
- EULAR responder (moderate and good combined) rate at Week 2 (Day 15)
- EULAR responder (only good) rate at Week 2 (Day 15)

Secondary Endpoints/Parameters:

- EULAR response at Week 1, 2, 3, 4, 6, 8 and 12.
- DAS28 mean and % change at Week 1, 2, 3, 4, 6, 8 and 12
- Time to first EULAR response (moderate/good)
- American College of Rheumatology (ACR) 20/50/70 response scores at Week 1, 2, 3, 4, 6, 8 and 12
- Tender joint counts at Week 1, 2, 3, 4, 6, 8 and 12
- Swollen joint counts at Week 1, 2, 3, 4, 6, 8 and 12
- Patient Pain and Global Visual Analog Score (VAS) score at Week 1, 2, 3, 4, 6, 8 and 12
- Investigator Global Visual Analog Score (VAS) score at Week 1, 2, 3, 4, 6, 8 and 12
- Short Form 36 (SF-36) to assess physical and mental component at Week 1, 2, 4, 6, and 12.
- Health Assessment Questionnaire (HAQ) at Week 1, 2, 3, 4, 6, 8 and 12.
- The Functional Assessment of Chronic Illness Therapy (FACIT) at Baseline, Week 4 and 6
- Health Economics Questionnaire at Week 12
- Maintenance of Improvement at 12 Weeks assessed during a blinded review by the Medical Monitor (MM) and Principal Investigator (PI) at the end of the study
- Pharmacokinetics (PK) assessment in subset of patient population at Baseline, Week 1, 2, 3, 4 and 6
- AEs (including glucocorticoid related AEs), AEs leading to withdrawal, AEs leading to discontinuation of medication, and AEs due to infusion reactions)
- Vital signs
- Physical examinations

- Laboratory
- ECG
- Assessment by monitoring cortisol levels at Screening, Baseline, 6 and 12 weeks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The study consists of 9 visits to the clinic in 14 Weeks; at each of these visits blood samples are taken; at each visit a physical examination (PE) will take place; at each visit the subjects have to fill out questionnaires. For details please see Table 2, Schedule of Assessments.

Nanocort, as a single infusion of 300 mg or two infusions of 150 mg each with a 6-10 or 14 Day interval between infusions, appears to be well tolerated by subjects. Overall, few adverse events (AEs) typically associated with the administration of glucocorticoids have been observed [5].

Too rapid an infusion of PEG-liposomal products could cause a pseudo-allergic infusion reaction. These acute infusion-related reactions, are typically characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest and throat, and/or hypotension, and are related to complement activation. The likelihood of the occurrence of such infusion reactions has been described for liposomes (empty placebo as well as drug-loaded) and is not unlike that for other colloidal formulations and biologics, with an incidence of about 5-10% of patients [5]. The slower infusion speed used in the later Nanocort trials has resulted in a lower infusion reaction incidence. This study will involve an even slower rate of infusion over a 2.5 hour period.

1. INTRODUCTION AND RATIONALE

Rheumatoid arthritis is a chronic, serious progressive and debilitating inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. RA is considered as an auto immune disease [6].

The current modern standard of care is based on the knowledge of the severity of the natural history of RA. Patients are treated early using aggressive treatment strategies, with methotrexate (MTX) as anchor drug, biological targeted therapies in those with inadequate response, and tight control aiming for remission and low disease activity [7], according to the 2012 American College of Rheumatology (ACR) Update [8] the European League Against Rheumatism (EULAR) recommendations [9] and European Medicines Agency (EMA) Guideline on clinical investigation of medicinal products other than Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for the treatment of rheumatoid arthritis (draft 2015 [10]).

Glucocorticoids (GCs) have been – and still are – a cornerstone in the treatment of rheumatic diseases for many decades [11, 12]. In RA, the general view is that GCs are to be used at the lowest doses possible in order to minimize their systemic exposure and their related side effects. In order to reach higher local concentrations of GCs, while minimizing potential systemic adverse effects, intra-articular (IA) injections of high dose GCs are frequently used in the management of RA.

However, it is impractical to inject multiple joints in a patient with an exacerbation of RA. Thus there is a clear and well established need for GCs to be administered in a way that multiple joints receive high local concentrations of the drug after a single systemic treatment while the healthy organ exposure to active drug upon such treatment remains in line with that of an established low systemic GC maintenance dosing schedule that is generally considered to be safe in RA. Nanocort is such a novel GC therapy.

Nanocort is being developed to enable selective local delivery of GC to sites of inflammation targeting all inflamed joints upon one or two IV administrations of liposomal entrapped prednisolone (as inactive sodium phosphate). Enclosing prednisolone in small, carefully designed lipid vesicles is designed to allow selective accumulation in inflamed tissues following IV administration. This effect is thought to occur by virtue of the locally increased permeability of blood vessel walls, while limiting systemic exposure down to acceptable levels.

To date, data are available for 65 subjects who have received Nanocort in single doses of up to 300 mg. Of most relevance for the proposed indication, an investigator-initiated, two-part

clinical trial (ENLA001) has been completed in 22 subjects with active RA, 14 received Nanocort. The first part of the study was an open-label, two dose level escalation (37.5 and 75 mg) in 3 subjects with each dose. The second part was a 12-Week, double-blind, parallel group comparison in 16 subjects of a single 150-mg IV dose of Nanocort and a single 120-mg IM dose of methylprednisolone (Depo-Medrol). Nanocort was found to be safe and well-tolerated and in the second part of the study, showed statistically significant reduction in the DAS28 when compared to Depo-Medrol. Data are also available from a clinical study (GLPG0303-CL-204) in 15 subjects with active multiple sclerosis (MS) in which doses of 300 mg single dose were administered to 8 subjects in total.

Other studies with Nanocort have been initiated in patients with atherosclerosis, peripheral artery disease, and ulcerative colitis. In addition, radio-labeled PEG liposomes, such as those in the Nanocort formulation, have also been successfully used for imaging in patients with RA, Inflammatory Bowel Disease (IBD) and other focal infection/inflammation in the body [13].

The safety and efficacy profile attributed to Nanocort warrant further clinical investigation of Nanocort for the treatment of RA, MS, and IBD. The population of patients to be enrolled in this trial with an exacerbation / flare of RA has been selected, as this is the population which is currently being treated with GC and is exceptionally well suited for a targeted, short term treatment approach with Nanocort.

2. OBJECTIVES

Primary Objective:

To assess efficacy and safety (treatment of signs and symptoms) of Nanocort in subjects with active rheumatoid arthritis who are experiencing a flare/exacerbation in comparison to a standard of care medication (Depo-Medrol).

Secondary Objective(s):

- To evaluate patient-reported outcomes in subjects with Active Rheumatoid Arthritis who are experiencing a flare/exacerbation receiving IV Nanocort as compared with subjects receiving IM injections of methylprednisolone acetate.
- To assess PK parameters, in a subset population from each treatment group.

3. STUDY DESIGN

This is a randomized, double-blind, double dummy, active controlled, parallel, multi-center study in which IV Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) will be compared with IM injection of methylprednisolone acetate (Depo-Medrol) to evaluate efficacy and safety. Each patient will receive treatment on Day 1 and Day 15 both an infusion and an IM injection containing either an active treatment or a dummy treatment. The total duration of the trial is 14 weeks maximum for each subject (up to 2 weeks of screening period and 12 weeks of treatment with follow up).

During this 14 weeks study, the dosage of any [redacted] should not be changed (in case the subject is receiving such treatment at screening).

The use of Depo-Medrol 120 mg IM for the control group and the short duration of treatment are selected in order to use standard of care treatment for exacerbations / flares in subjects with RA. Furthermore, the total GC exposure is the same in the 120 mg Depo-Medrol and 150 mg Nanocort arms. Additional Nanocort 75 mg arm is included.

4. STUDY POPULATION

4.1 Population

The study will be conducted at approximately 25 sites in the Netherlands, Belgium and the Czech Republic. Sites will be selected based on previous study experience in RA and accessibility to study required populations. It is expected that each research centre will be able to identify sufficient subjects that meet all the inclusion and exclusion criteria.

The study population will consist of male and female subjects (≥ 18 years old) with active RA who are experiencing a flare / exacerbation defined as recently switched from a period with -well documented- remission or low disease activity to an active disease (DAS28 ≥ 3.2). This documentation is either based on available detailed DAS28 values (increase in DAS28 > 1.2 or > 0.6 if DAS28 ≥ 3.2 compared to last DAS28 measurement (maximum 06 months before), or on a clear description of the previous low disease state by the treating physician (maximum 06 months before). The increase in disease activity has to be RA related.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1) Male or female ≥ 18 years old.
2) Known Diagnosed RA according to the revised 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria. Secondary Sjögren's syndrome with RA is permitted.
3) Male and female subjects recently switched from a period with -well documented- remission or low disease activity to an active disease (DAS28 ≥ 3.2). This documentation is either based on available detailed DAS28 values (increase in DAS28 > 1.2 or > 0.6 if DAS28 ≥ 3.2 compared to last DAS28 measurement (maximum 06 months before), or on a clear description of the previous low disease state by the treating physician (maximum 06 months before). The increase in disease activity has to be RA related.
4) Willing and able to comply with the study protocol visits, assessments and accessible for follow up.
5) Subjects naïve to treatment and/or currently not treated for at least 8 Weeks prior to the Screening Visit and willing to continue without non-study treatment for 12 Weeks, or subjects on stable treatment with DMARD (including biologicals) for at least 8 Weeks prior to the Screening Visit and willing to continue current stable treatment for 12 Weeks.

6) Subjects able and willing to give written informed consent (or legally acceptable representative or impartial witness when applicable) and is available for entire study.
7) Subjects of child bearing potential should be non-lactating and must be practicing an acceptable method of birth control as judged by the Investigator. Medically acceptable methods of birth control include bilateral tubal ligation or the use of either a contraceptive implant, a contraceptive injection (e.g., Depo-Provera™), sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject), an intrauterine device, vasectomized partner, an oral contraceptive taken continually within the past three months and which the subject agrees to continue using during the study
   - To adopt another birth control method, or a double-barrier method which consists of a combination of any two of the following: diaphragm, cervical cap, condom, or spermicide at least 2 months prior to study entry and must continue to use contraception for the duration of the study
   - Subjects who are postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy has been performed on the subject) may participate in study.
   - All female subjects of child-bearing potential must have a negative urine pregnancy test
8) Male subjects enrolled in the study are advised to prevent passage of semen to their sexual partner during intercourse using acceptable methods as judged by the investigator, like condoms, , abstinence or vasectomy.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1) Rheumatic autoimmune disease other than RA, e.g., systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), scleroderma, polymyositis.
2) Current inflammatory joint disease other than RA (e.g., gout, reactive arthritis, psoriatic arthritis, spondyloarthritis, Lyme disease, osteoarthritis).
3) Subjects who are pregnant or intend to become pregnant during the study.
4) Have a family history (more than one first degree relative) of multiple thrombotic events (more than one per person) or a personal history of any venous or arterial

thrombotic event including deep vein thrombosis, stroke, myocardial infarction, pulmonary embolus, and peripheral arterial thromboembolic events or abnormal ECG which may impact the subject's safety as per Investigator's opinion.

5) Subject with positive hepatitis panel (including hepatitis B surface antigen [HBsAg], and / or anti-hepatitis B core antibodies, and / or hepatitis C virus antibody [anti-HCV]), and / or a positive Human immunodeficiency virus (HIV) antibody screen, based on the current medical data of the patient. Subjects with active or latent tuberculosis are also excluded.
6) Abnormal hepatic function [alanine aminotransferase (ALT)/aspartate aminotransferase (AST) or bilirubin > 2 x upper limit of normal] at the time of the Screening Visit.
7) Abnormal renal function [Blood Urea Nitrogen (BUN) or creatinine >1.25 x upper limit of normal] at the time of the Screening Visit.
8) Clinically significant out-of-range values on hematology panel, at discretion of the PI.
9) Treatment with oral, rectal or injectable (including intra-articular) glucocorticoids (GCs) within 8 Weeks prior to Screening Visit. Inhaled glucocorticoids are allowed. Topical steroids are allowed, however subjects should not have received more than 100 gram of a mild to moderate topical corticosteroid cream per Week, 50 gram of a potent corticosteroid cream per Week or 30 gram of a very potent topical corticosteroid cream per Week in the 4 Weeks prior to the Screening Visit.
10) Subjects who have received an investigational drug within 30 Days prior to the Screening visit.
11) Previous treatment with IV gamma globulin, plasmapheresis or Prosorba® column within 3 months prior to Screening.
12) Known sensitivity to any component of the study drug or previous hypersensitivity reaction or other clinically significant reaction to IV medications, biologic therapy or IV radiocontrast agents.
13) Contraindication for glucocorticoids as judged by Investigator.
14) Subjects who have previously received Nanocort.
15) Neuropathies or other painful conditions that might interfere with pain evaluation, as judged by the Investigator.
16) Active infection requiring systemic treatment.
17) Planned surgery during the study period or had undergone major surgery within the 60 Days prior to the Screening visit.
18) Requirement for immunizations or vaccinations during the treatment period.
19) Subjects with poor peripheral venous access as per Investigator or site personnel opinion.

20) History of substance abuse or alcohol abuse.

Additional exclusion criteria for subjects participating in PK subset study:

Blood donation by subjects within 6 months before screening.

4.4 Sample size calculation

A total of 330 subjects will be enrolled and randomized into 3 groups of 110 subjects.

The EULAR response will be considered as primary parameter.

There is a special interest in the percentage of subjects with an EULAR response category of good or moderate (good and moderate combined) and the percentage of subjects with an EULAR response category of only good. These subjects will be called **EULAR responders** and **EULAR good-responders**, respectively.

[redacted]

Primary endpoint:

- the percentage of EULAR responders (good and moderate combined) at Day 8

Key secondary endpoints:

- The percentage of EULAR good-responders at Day 8
- The percentage of EULAR responders at Day 15
- The percentage of EULAR good-responders at Day 15

[redacted]

The sample size calculation for this study is based on group comparisons of EULAR responder rates (Nanocort 150 mg compared to Depo-Medrol® and Nanocort 75 mg compared to Depo-Medrol®) at Day 8. The study is called positive if one of the primary null hypotheses will be rejected. [redacted]

The following primary null hypotheses will be considered:

H0,1 : EULAR responder rate at Day 8 for Nanocort 150 mg = EULAR responder rate at Day 8 for Depo-Medrol®

H0,2 : EULAR responder rate at Day 8 for Nanocort 75 mg = EULAR responder rate at Day 8 for Depo-Medrol®

Taking a drop-out rate of approximately 10% into consideration, a sample size of 110 subjects per treatment arm will be sufficiently large to show superiority of Nanocort compared to Depo-Medrol® in EULAR responders at Day 8 and to assess the safety of Nanocort in this study.

5. TREATMENT OF SUBJECTS

5.1 Investigational medicinal products

Eligible subjects will be randomized to one of three treatment groups:

- Nanocort 75 mg IV infusion and IM saline injection, or
- Nanocort 150 mg IV infusion and IM saline injection, or
- Depo-Medrol 120 mg IM injection and IV saline infusion.

Subjects in this trial will be randomized to receive either Nanocort (75 mg/infusion or 150 mg/infusion) administered as an IV infusion, or 120 mg methylprednisolone acetate (Depo-Medrol®) administered as an IM injection. Subjects will receive treatment on Day 1 and Day 15 with additional study visits on Weeks 1, 2, 3, 4, 6, 8 and 12. Compliance will be recorded after dosing of Investigational Medicinal Product (IMP) at Day 1 and Day 15 (week 2).

IV infusion (either Nanocort/Placebo) will be administered over approximate 2.5 hours, with an increasing infusion rate over the whole infusion period. If required, infusion rate can be modified in case of infusion related reactions as per PI opinion. A detailed instruction will be documented the in the Investigational Medicinal Product (IMP) manual.

5.1.1 Nanocort arm

Prior to Nanocort administration, the contents of the requisite number of vials will be diluted up to 500 mL with normal saline (NaCl 0.9% w/v) and will be administered as IV infusion

In addition, these patients will receive IM normal saline (as placebo) in 3 ml in the same visit.

5.1.2 Depo-Medrol arm

On Day 1 and Day 15 subjects will receive IM injection of Depo-Medrol (3 ml) and 500 ml normal saline (as placebo) as IV infusion in the same visit.

The details of the preparation and administration of the IMP will be documented in the IMP manual.

5.1.3 Blinding

The study will be performed in a double blind, double dummy fashion. Each patient will receive an infusion and an IM injection containing either an active treatment or a dummy treatment. Opaque IV lines, sleeved bags and opaque syringes will be used to maintain blinding. The IMP preparation will be done by an independent unblinded person (pharmacist or designated person) in order to keep the Investigator and other site personnel blinded.

Proper care has to be taken so that the patient's treatment will not be disclosed to the patient, Investigator or other site personnel.

5.2 Use of co-intervention

Any medication the subject takes other than the study drug is considered a concomitant medication (co-medication). All co-medications must be recorded in the Electronic Case Report Form (eCRF). The following information must be recorded in the eCRF for each co-medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF. The subject should not take any concomitant treatment without the Investigator's knowledge. Investigator will instruct patients about co-medications and diet if required.

At Screening, subjects will be asked to provide details of all medications they have taken during the last 8 weeks. At each subsequent study visit (as listed in the Schedule of Assessments), subjects will be asked what co-medications they are currently taking.

During the study co-medications may be administered at the discretion of the Investigator in order to provide the subject with the best possible medical care. However, it is recommended that changes in ongoing treatments or introduction of new therapies are kept to a minimum. The risk/benefit to the subject should be carefully assessed and consideration given to the timing of any necessary introductions during the study period.

5.2.1 Allowed Medications

Co-medications that are allowed during this study include:

- Concomitant therapies taken for the long term treatment of pre-existing conditions (as per Investigator's opinion) may be continued during the study. However, these should be stabilized prior to entry and continued wherever practical without variation of dose or regimen during the study.
- Prescription medications for contraception and/or those medications deemed acceptable by the Investigator and Sponsor, or designee.
- Topical glucocorticoid GC creams are allowed, however subjects should not receive more than 100 gram of a mild to moderate topical corticosteroid cream per Week, 50 gram of a potent corticosteroid cream per week or 30 gram of a very potent topical corticosteroid cream per week in the 4 weeks prior to the Screening Visit and throughout the duration of the study.

- Inhaled glucocorticoids are allowed.
- Stable treatment with DMARD for at least 8 weeks prior to the Screening Visit and willing to continue current treatment for 12 weeks/throughout the study (this includes biologicals).
- Rituximab is only allowed when on a fixed dosing scheme of every 6 months.

5.2.2 Prohibited Medications

The following medication use is restricted and/or will exclude the subject from enrolment in this trial:

- Exposure to an experimental treatment or use of investigational product within the past 30 days prior to Screening, or is still within a washout period of a previous clinical trial.
- Last treatment with oral, rectal or injectable (including intra-articular) glucocorticoids (GCs) must be discontinued for at least 8 weeks prior to Screening Visit and may not be taken throughout the duration of the study.
- Previous treatment with IV gamma globulin, plasmapheresis or Prosorba® column within 3 months prior to screening and during the study.
- Systemic antibiotics and/ or anti-viral medications for treatment of an active infection required at the time of screening.
- Immunizations or vaccinations during the study period.
- Medications that may cause drug-drug interactions with methylprednisolone in opinion of investigator

5.2.3 Escape medication

Investigator can use medicines in safeguard of patient if required.

5.2.4 Other RA medication

All subjects will be followed for 12 weeks. Subjects who do not reach at least a moderate EULAR response at week 2 or at any visit thereafter, may receive other RA medication. In this case, several QoL measurements may be skipped, see footnote in Table 2, Schedule of Assessments. The infusion at week 2 will take place and the patients remain in the study for the remaining visits for safety follow up.

6. INVESTIGATIONAL MEDICINAL PRODUCT

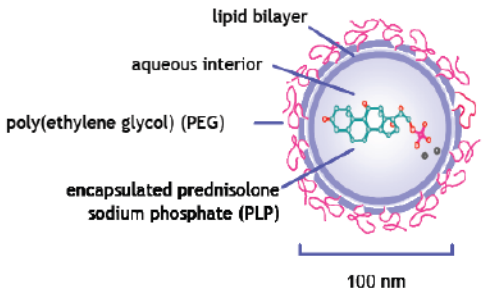
6.1 Name and description of investigational medicinal product(s)

Nanocort is provided as a sterile, white to off-white, translucent liposomal dispersion for IV infusion, in 20 mL glass, single use vials. Each vial contains nominally 5.0 mg/mL +/- 5% Prednisolone sodium phosphate, encapsulated inside the liposomes, dispersed in 10% w/v sucrose solution, buffered with phosphate buffer at a pH of 7.4 and a tonicity range of 280 to 400 mOsm/kg. The product needs to be stored refrigerated between 2 and 8 °C. Freezing needs to be avoided.

Name of Finished Product:

Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort)

Figure 1. Drug Product Diagram



Description of Investigational Medicinal Product:

Nanocort is a novel formulation containing prednisolone sodium phosphate [PhEur] as the drug substance encapsulated in PEGylated liposomes of approximately 100 nm (range 80 to 120 nm) that comprise a lipid bilayer of dipalmitoyl phosphatidyl choline (DPPC), cholesterol, and mPEG2000-distearoyl phosphatidyl ethanolamine (mPEG2000-DSPE) in a mass ratio of approximately 3.5:1:1. Coating of the liposome lipid bilayer with PEG improves the properties and performance of the formulation, including physical stability and prolonged circulation time in vivo. The lipid bilayer encloses an aqueous compartment in which the water-soluble sodium phosphate derivative of prednisolone is entrapped. The proposed formulation also includes the compendial excipients sucrose, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate, absolute ethanol (removed during diafiltration process), and Water for Injection.

6.2 Summary of findings from non-clinical studies

Nonclinical pharmacology studies with Nanocort have been performed in rodent arthritis models including rat adjuvant-induced arthritis (AIA) and mouse collagen-induced arthritis (CIA) [15, [redacted] Histology of the inflamed joints showed a beneficial effect both at the level of inflammation (complete resolution of joint cavity exudate and inflammatory cellular infiltrate) and a significant delay of the process of cartilage erosion.

Please refer to Investigator's Brochure (IB) for more detailed information on the non-clinical studies.

6.3 Summary of findings from clinical studies

Based on the five studies so far in different indications, clinical safety data on Nanocort are currently available for 65 patients (14 with RA and 8 with MS, 20 with Atherosclerotic Disease, 7 with Peripheral Artery Disease and 16 with Acute Ulcerative Colitis). In these studies Nanocort was found to be safe and well-tolerated. Approximately 9.7% of patients in studies with Nanocort to date have experienced an infusion reaction (verbatim term) and/or infusion related reaction (verbatim term) and 2.7% of patients experienced an acute infusion reaction (verbatim term).

6.4 Summary of known and potential risks and benefits

The risk-benefit assessment of the administration of Nanocort to humans is informed by preclinical and clinical evaluations [19]. Taken together these data provide a risk-benefit profile favourable to study Nanocort compared to the standard of care, Depo-Medrol, for use in RA.

6.4.1 Evaluation of the Risks

Too rapid an infusion of Nanocort could cause a pseudo-allergic infusion reaction. The slower speed used in the ongoing trials has resulted in a low infusion reaction incidence. The likelihood of the occurrence of infusion reactions has been described for liposomes (empty placebo as well as drug-loaded) and is not unlike that for other colloidal formulations and biologics, with an incidence of about 5-10% of patients.

Due to the small overall sample size, which includes uncontrolled study data, it is difficult to assess the relationship of the observed AEs to Nanocort at this time of development. The

following AEs were observed in > 5% of subjects: ALT increased, AST increased, blood lactate dehydrogenase increased, chills, cough, diarrhea, dizziness, fatigue, glycosuria, haematoma, headache, hot flush, hyperhidrosis, infusion related reaction, nasopharyngitis, nausea, paraesthesia, pharyngolaryngeal pain, pyrexia, rash, skin ulcer, and sleep disorder.

However, many of these AEs may not have a pathophysiological relationship with Nanocort. At this time, with the limited exposure to Nanocort, there have not been any significant changes in the assessment of benefit or risk to subjects in the clinical trials that have not been previously described. There are no emerging potential safety issues that require a change in the current development program or require additional assessments in the on-going studies or in any subsequent studies.

6.5 Description and justification of route of administration and dosage

Nanocort® (Pegylated Liposomal Prednisolone Sodium Phosphate) is provided as a sterile, white to off-white, translucent liposomal dispersion for IV infusion, in 20 mL glass, single use vials.

Route of administration: The IV route is selected for this study based on previous study experience.

Dose: The 75 mg and 150 mg doses are selected based on prior experience with Nanocort.

6.6 Dosages, dosage modifications and method of administration

Dosages and method of administration

Subjects in this trial will be randomized to receive either an IM injection of 120 mg methylprednisolone acetate (Depo-Medrol), or 75 mg/infusion of Nanocort administered as an IV infusion or 150 mg/infusion of Nanocort administered as an IV infusion, on Day 1 and 15.

Nanocort will be infused over approximately 2.5 hours. The details of Nanocort preparation and administration is given in IMP manual.

If an infusion reaction occurs, the infusion rate can be lowered or the infusion can be temporarily halted. The infusion reactions can be treated with standard of care and infusion can be resumed as per Investigator's opinion. If an infusion reaction occurred during the first infusion, the subject will receive standard pre-treatment before the start of the second infusion.

6.7 Preparation and labelling of Investigational Medicinal Product

Prior to Nanocort administration, the contents of the requisite number of vials will be diluted with normal saline (NaCl 0.9% w/v).

Example Label:

20 mL vial label:
Protocol No: CLR_15_05
Contents: Nanocort – 5 mg/mL
Solution for Intravenous use 20 mL per vial
Batch/Lot #: XXXXXXX

FOR CLINICAL TRIAL USE ONLY
Store at 2-8°C Vial Number: XXXX
Expiration date/Retest Date: DD/MMM/YYYY
Sponsor: Sun Pharma Global FZE
ADDRESS: Sharjah, United Arab Emirates

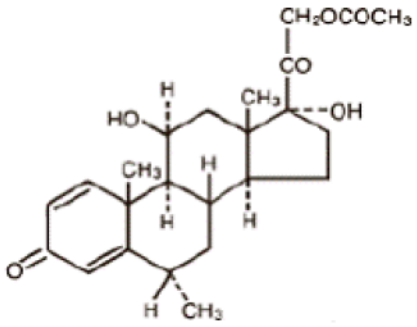
7. COMPARATOR

7.1 Name and description of comparator product(s)

DEPO-MEDROL is an anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue or intralesional injection.

DEPO-MEDROL Sterile Aqueous Suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water [18].

The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21 (acetyloxy)-11,17-dihydroxy-6-methyl-,(6α,11β) and the molecular weight is 416.51. The structural formula is represented below:



See Package Insert for Depo-Medrol.

7.2 Description and justification of route of administration and dosage

DEPO-MEDROL will be administered by IM injection at the dose of 120 mg. This dosage was selected as this is the standard of care treatment for exacerbations / flares. Furthermore, the 120 mg IM of Depo-Medrol is equipotent to 150 mg IV of Nanocort [19].

7.3 Dosages, dosage modifications and method of administration

Placebo: All subjects will also receive saline (placebo): either IM sterile saline or IV sterile saline on Day 1 and Day 15. Therefore, subjects that are randomized to receive one of the 2 doses of Nanocort will also receive an IM injection of placebo (0.9% saline), and the subjects that are randomized to receive IM injection of Depo-Medrol will receive an IV infusion of placebo (0.9% saline). Appropriate care will be taken to use opaque lines for drug administration equipment.

Subjects in this trial will be randomized to receive an IM injection of 120 mg methylprednisolone acetate (Depo-Medrol), or 75 mg/infusion of Nanocort administered as an IV infusion or 150 mg/infusion of Nanocort administered as an IV infusion, on Day 1 and 15.

7.4 Preparation and labelling of comparator

DEPO-MEDROL® is an anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue or intralesional injection. It is available in three strengths: 20 mg/mL; 40 mg/mL; 80 mg/mL. Sodium Chloride was added to adjust tonicity. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. The pH of the finished product remains within the USP specified range; e.g., 3.5 to 7.0. See Package Insert for additional information. Labelling shall be performed separately for Depo-Medrol.

7.5 Use of saline

The dummy product (commercially available Saline 0.9%) will be purchased by the Sponsor and supplied to the clinical sites. All subjects will also receive placebo either IM saline or IV saline on Day 1 and Day 15. Therefore, subjects that are randomized to receive one of the 2 doses of Nanocort will also receive an IM injection of placebo (0.9% saline), and the subjects that are randomized to receive IM injection of Depo-Medrol will receive an IV infusion of placebo (0.9% saline).

8. METHODS

8.1 Study parameters/endpoints

The objective of the current trial is to assess efficacy and safety (treatment of signs and symptoms) of Nanocort in subjects with active rheumatoid arthritis who are experiencing a flare/exacerbation in comparison to a standard of care medication. Efficacy will be measured by comparing the therapeutic effect of 75 mg or 150 mg IV administration Nanocort with the therapeutic effect of an IM administration of 120 mg methylprednisolone (Depo-Medrol) as measured by the EULAR response as well as other measures of RA activity.

8.1.1 Main study parameter/endpoint

The Primary parameter that will be measured is the EULAR response at Week 1 (Day 8).
Primary Endpoint: EULAR responder (moderate and good combined) rate at Week 1 (Day 8)

8.1.2 Key Secondary study parameters/endpoints

- EULAR responder (only good) rate at Week 1 (Day 8)
- EULAR responder (moderate and good combined) rate at Week 2 (Day 15)
- EULAR responder (only good) rate at Week 2 (Day 15)

Secondary study parameters/endpoints

The secondary endpoints that will be measured are:

- EULAR response at Week 1, 2, 3, 4, 6, 8 and 12
- DAS28 mean and % change at Week 1, 2, 3, 4, 6, 8 and 12
- Time to first EULAR response (moderate/good)
- ACR 20/50/70 response scores at Week 1, 2, 3, 4, 6, 8 and 12
- Tender joint counts at Week 1, 2, 3, 4, 6, 8 and 12
- Swollen joint counts at Week 1, 2, 3, 4, 6, 8 and 12
- Patient pain and Global Visual Analog Score (VAS) score at Week 1, 2, 3, 4, 6, 8 and 12
- Investigator Global Visual Analog Score (VAS) score at Week 1, 2, 3, 4, 6, 8 and 12
- Short Form 36 (SF-36) to assess physical and mental component at Week 1, 2, 4, 6, and 12.
- Health Assessment Questionnaire (HAQ) at Week 1, 2, 3, 4, 6, 8 and 12.
- The Functional Assessment of Chronic Illness Therapy (FACIT) at Baseline, Week 4 and 6
- Health Economics Questionnaire at Week 12

- Maintenance of Improvement at 12 Weeks assessed during a blinded review by the Medical Monitor (MM) and Principal Investigator (PI) at the end of the study
- AEs (including glucocorticoid related AEs, AEs leading to withdrawal, AEs leading to discontinuation of medication, and AEs due to infusion reactions)
- Vital signs
- Physical examinations
- Laboratory
- ECG
- [redacted]
- Assessment by monitoring cortisol levels at Screening, Baseline, 6 and 12 weeks

8.2 Randomisation, blinding and treatment allocation

Subject randomization will take place before the start of administration of the IMP.

Subjects will be randomized in a 1:1:1 ratio to the three treatment arms and stratified by site.

Randomization of the subjects will be performed by an Interactive Web-based Randomization System (IWRS) by an independent party. The randomization number will be recorded on the eCRF. Once the numbers have been assigned they cannot be reassigned.

Subjects in this trial will be randomized in a 1:1:1 ratio to receive one of three dose groups:

- **Nanocort 75 mg** IV infusion and IM saline injection on Day 1 and Day 15, or
- **Nanocort 150 mg** IV infusion and IM saline injection on Day 1 and Day 15, or
- **Depo-Medrol 120 mg** IM injection and IV saline infusion on Day 1 and Day 15

Blinding:

Prior to the start of the study, a copy of the master randomization code will be stored in confidential manner up to the unblinding after database lock. A separate unblinded Pharmacovigilance Medical Reviewer and unblinded Pharmacovigilance Associate will be available for triage, review and submission of safety events.

Any reported Suspected Unexpected Serious Adverse Reactions (SUSARs) will be triaged by the Medical Monitor in a blinded fashion and forwarded for full processing to the unblinded Medical Reviewer and unblinded Pharmacovigilance Reviewer for processing and reporting to the Competent Authority (CA) and Independent Ethics Committee (IEC) per regulations.

Unblinding to Investigator and subject will occur only after database closure at the end of the study. The study blind will only be broken after database lock except in the case of

emergency to protect subject's safety. The code may be broken in case of an emergency, preferably after discussion with the MM. Any code break will be recorded and a copy retained within the study file.

The blind will be preserved throughout the study unless, in the opinion of the Investigator, the lack of this information places the subject at undue risk. In general, this will occur only if an adverse event occurs for which the subject's physician requires knowledge of the treatment assigned. In this case, the Sponsor should be notified as soon as possible and un-blinded information for the subject's treatment group will be provided.

Premature unblinding of study drug may occur to reveal whether a subject has been receiving Nanocort or Depo-Medrol. This should occur only in an emergency and if the information is considered by the Investigator (or other treating physician) as medically necessary. If unblinding occurs prior to notification of the Medical Monitor the circumstances leading to the unblinding must be clearly documented and promptly reported by telephone or in writing to the Medical Monitor. Unblinding will be performed by the IWRS responsible person.

8.3 Study procedures

The Schedule of Assessments (Table 2) included in the protocol summarizes the timing of the efficacy and safety measurements.

The Day of the first dose administered to a subject is considered Day 1 for that individual subject. Other study Days are calculated with Day 1 as the reference point. Screening will consist of period up to 2 Weeks (14 Days) and those subjects that are still eligible after the screening visit will be randomized to one of the three treatment groups.

Treatment will be given on Day 1 and Day 15. The patient will be followed up for 12 Weeks or End of Study visit. In the event of early termination, subjects are asked to return for the Week 12 assessments if possible. Otherwise, the subjects are assessed as per Week 12 assessment schedule on the Day of termination. Infusion related reactions will be monitored during the infusion and at the end of infusion.

Physical Examination

A full physical examination should include: General appearance, Skin, Head and Neck, Eyes-Ears-Nose, Throat, Lymph Nodes palpation, Cardiovascular, Lungs & Chest, Abdomen, Musculoskeletal, and Neurological Function. All other body systems should be assessed at the Investigator's discretion. A full physical examination will be done at Screening, Baseline

and End of study. For remaining visits it will be up to the judgement of the Investigator if a full or abbreviated exam is completed.

Vital Signs

Vitals signs will be taken supine (for 5 minutes) and include heart rate, respiratory rate, blood pressure (BP), and temperature. The method of temperature assessment must remain consistent for each individual subject throughout the study.

Subject blood pressure and heart rate will be measured using an automatic device (whenever possible) after the subject has rested (supine) comfortably for 5 min. Vital signs will be measured at the time points specified in the Schedule of Assessments (Table 2).

Weight will be recorded as per Table 2.

Disease Activity Score in 28 Joints (DAS28)

The DAS28 is a composite index for measuring disease activity in RA and is calculated at each study visit. The index includes swollen (range 0-28) and tender joint counts (range 0-28), acute phase response erythrocyte sedimentation rate (ESR), and general health status (range 1-100). The DAS28, which uses a 28 joint count including shoulders is derived from the original DAS, which includes a 44 swollen joint count. The DAS28 has been validated in RA. The index is calculated using the formula from the EULAR website: http://emeunet.eular.org/links.cfm?catID=19.

The DAS28 ranges from 0 to 9.3, where higher scores represent higher disease activity.

Joint Tenderness and Swelling Assessments

An assessor at each site will be used to evaluate tenderness and swelling of the 28 joints specified by the DAS28 scoring system. Scoring for each joint will be based on whether or not the joint is swollen (1=yes, 0= no) and whether the joint is tender (1=yes, 0= no). The CRF will also have the options Not done and Not Evaluable. Evaluations will be done at all study visits.

Health Assessment Questionnaire (HAQ)

The HAQ is a patient-reported outcomes (PRO) questionnaire based on 5 patient-centered dimensions; disability, pain, medication effects, costs of care, and mortality. The version used for this trial is the “short” or 2-page HAQ comprised of the HAQ disability module and the global and pain visual analog scales [20]. The HAQ may be completed directly by the subject or by an interviewer. HAQ will be collected at Baseline and all post dose study visits. *[Appendix 14.2]*

Short Form-36 (SF-36) Survey

The Short Form (36) Health Survey is a patient-reported survey of patient health [21]. The SF-36 is a measure of health status. SF-36 surveys may be completed directly by the subject or by an interviewer. SF-36 surveys will be collected at Baseline and Week 1, 2, 4, 6, and 12. *[Appendix 14.1]*

Functional Assessment of Chronic Illness Therapy (FACIT) Score

"FACIT" (Functional Assessment of Chronic Illness Therapy) was adopted as the formal name of the measurement system in 1997 to portray the expansion of the familiar "FACT" (Functional Assessment of Cancer Therapy) questionnaires into other chronic illnesses and conditions [22]. Questionnaires may be completed directly by the subject or by an interviewer. The FACIT questionnaire will be collected at Baseline, Week 4 and Week 6. *[Appendix 14.3]*

EULAR Response

Comparing the DAS28 from one patient on two different time points, it is possible to define moderate or good response [14]. The EULAR response criteria are defined as follows:

DAS28 improvement → / Present DAS28↓	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2	good response	moderate response	no response
> 3.2 and ≤ 5.1	moderate response	moderate response	no response
> 5.1	moderate response	no response	no response

The EULAR response will be calculated at all visits after Baseline.

American College of Rheumatology 20/50/70 (ACR 20/50/70)

ACR score is a scale to measure change in rheumatoid arthritis symptoms. It is named after the American College of Rheumatology. Different degrees of improvement are referred to as ACR20, ACR50, ACR70. The following definition of improvement was selected: 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant [23]. ACR 50 and ACR 70 criteria are defined in a manner similar to that for ACR 20, but with improvement of at least 50 percent and 70 percent in the individual measures, respectively.

Visual Analog Scale (VAS)

The visual analogue scale or visual analog scale (VAS) is a psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective

characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points. Four VAS measurements will be at each study visit; the subject will assess their current pain level and general health, the subject will assess their RA Activity levels, and a trained blinded site evaluator will independently assess the subjects RA Activity levels.

Subjects will be given an explanation on use of different scales at screening.

8.3.1 Overview of Assessments by Study Day

Screening Visit (up to 14 Days prior to dosing)

- Informed Consent
- Medical and surgical history including history of RA diagnosis
- Demographic information [date of birth, race, height, smoking history, Rheumatoid Factor (RF)]
- Inclusion/exclusion criteria
- Previous and all current drug record review
- Full physical examination
- Vital signs supine for 5 minutes (heart rate, blood pressure, respiration rate and body temperature)
- Weight
- 12 lead Electrocardiogram (ECG)
- Visual Analog Scale (VAS) experience of pain (patient) and General Health
- VAS Rheumatoid Arthritis (RA activity patient's and Investigator's evaluation)
- Tender joint counts
- Swollen joint counts
- DAS28
- Disease flare
- Extensive laboratory:
    - Hematology: Hemoglobin (Hgb), Hematocrit (HCT), Red blood cells (RBC), White blood cells (WBC), differential count, platelet count, erythrocyte sedimentation rate (ESR)
    - Chemistry: Sodium (Na^+), potassium (K^+), chloride, total bilirubin, alkaline phosphatase (ALP), ALT [Serum glutamic pyruvic transaminase (SGPT)], AST [Serum glutamic oxaloacetic transaminase (SGOT)], Gamma Glutamyl Transpeptidase (GGT), Lactate dehydrogenase (LDH), C-

reactive protein (CRP), Creatinine Kinase (CK), Blood Urea Nitrogen (BUN), creatinine, glucose, uric acid, calcium (Ca++), phosphorous, total protein, albumin, Hemoglobin A1c (HbA1C), cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, osteocalcin and serum cortisol

  - Urinalysis: Glucose, N-telopeptide and creatinine

- Urine Pregnancy Test (as applicable)
- Tuberculosis test : QuantiFERON TB-Gold test (QFT) (as per local regulation)

Baseline Visit (Day 1)

- Full Physical examination
- Vital signs supine for 5 minutes (heart rate, blood pressure, respiration rate and body temperature)
- Adverse events
- Concomitant medication
- Visual Analog Scale (VAS) experience of pain (patient) and RA activity, also recorded in patient diary on Day 2, 4 and 6
- VAS Rheumatoid Arthritis RA activity Investigator's evaluation and patient General Health)
- Tender joint counts
- Swollen joint counts
- DAS28
- Functional Assessment of Chronic Illness Therapy (FACIT)
- Short Form 36 (SF-36) to assess physical and mental component and the Health Assessment Questionnaire (HAQ)
- Extensive laboratory (fasting):
  - Hematology: Hgb, HCT, RBC, WBC, differential count, platelet count, ESR
  - Chemistry: Sodium, potassium, chloride, total bilirubin, ALP, ALT (SGPT), AST (SGOT), gamma GT (GGT), LDH, CRP, CK, BUN, creatinine, glucose, uric acid, calcium (Ca++), phosphorous, total protein, albumin, HbA1C, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, osteocalcin and serum cortisol
  - Urinalysis: Glucose, N-telopeptide and creatinine
- Urine pregnancy test (as applicable)
- Re-Assess eligibility for enrollment

- Randomization
- Treatment / Dosing

[redacted]

Week 1 (Day 8±1), Week 3 (Day 22±2), Week 4 (Day29±2)

- Physical examination
- Vital signs supine for 5 minutes (heart rate, blood pressure, respiration rate and body temperature)
- Adverse events
- Concomitant medication
- EULAR and ACR Response
- VAS experience of pain (patient) and General Health
- VAS Rheumatoid Arthritis (RA activity patient's and Investigator's evaluation)
- Tender joint counts
- Swollen joint counts
- DAS28
- HAQ
- SF-36 at Week 1 and Week 4
- FACIT at Week 4
- Limited laboratory:
    - Hematology: Hgb, HCT, RBC, WBC, differential count, platelet count, ESR
    - Chemistry: Sodium, potassium, chloride, ALT, CRP, creatinine, glucose, HbA1C, HDL-cholesterol, LDL cholesterol, triglycerides and serum cortisol
    - Urinalysis: Glucose

[redacted]

Week 2 (Day 15±1)

- Physical examination
- Vital signs supine for 5 minutes (heart rate, blood pressure, respiration rate and body temperature)
- Adverse events
- Concomitant medication
- EULAR and ACR Response
- VAS experience of pain (patient) and RA activity, also recorded in patient diary on Day 16, 18 and 20

- VAS Rheumatoid Arthritis RA activity Investigator's evaluation and patient General Health
- Tender joint counts
- Swollen joint counts
- DAS28
- SF-36 and HAQ
- Limited laboratory:
    - Hematology: Hgb, HCT, RBC, WBC, differential count, platelet count, ESR
    - Chemistry: Sodium, potassium, chloride, ALT, CRP, creatinine, glucose, HbA1C, HDL-cholesterol, LDL cholesterol, triglycerides and serum cortisol
    - Urinalysis: Glucose
- Urine Pregnancy Test (as applicable)
- Treatment / Dosing

[redacted]

Week 6 (Day 43±3)

- Physical examination
- Vital signs supine for 5 minutes (heart rate, blood pressure, respiration rate and body temperature)
- Adverse events
- Concomitant medication
- EULAR and ACR Response
- Visual Analog Scale (VAS) experience of pain (patient) and General Health
- VAS Rheumatoid Arthritis (RA activity patient's and Investigator's evaluation)
- Tender joint counts
- Swollen joint counts
- DAS28
- SF-36 and HAQ
- FACIT
- Extensive laboratory (fasting):
    - Hematology: Hgb, HCT, RBC, WBC, differential count, platelet count, ESR
    - Chemistry: Sodium, potassium, chloride, total bilirubin, ALP, ALT (SGPT), AST (SGOT), gamma GT (GGT), LDH, CRP, CK, BUN, creatinine, glucose, uric acid, calcium (Ca++), phosphorous, total protein, albumin, HbA1C, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, osteocalcin and serum cortisol

- Urinalysis: Glucose, N-telopeptide and creatinine

[redacted]

Week 8 (Day 57±3)

- Physical examination
- Vital signs supine for 5 minutes (heart rate, blood pressure, respiration rate and body temperature)
- Adverse events
- Concomitant medication
- EULAR and ACR Response
- VAS experience of pain (patient) and General Health
- VAS Rheumatoid Arthritis (RA activity patient's and Investigator's evaluation)
- Tender joint counts
- Swollen joint counts
- DAS28
- HAQ
- Limited laboratory (fasting):
  - Hematology: Hgb, HCT, RBC, WBC, differential count, platelet count, ESR.
  - Chemistry: Sodium, potassium, chloride, ALT, CRP, creatinine, glucose, HbA1C, HDL-cholesterol, LDL cholesterol, triglycerides and serum cortisol
  - Urinalysis: Glucose

Week 12 (Day 85± 3) (End of Study/ Early Termination)

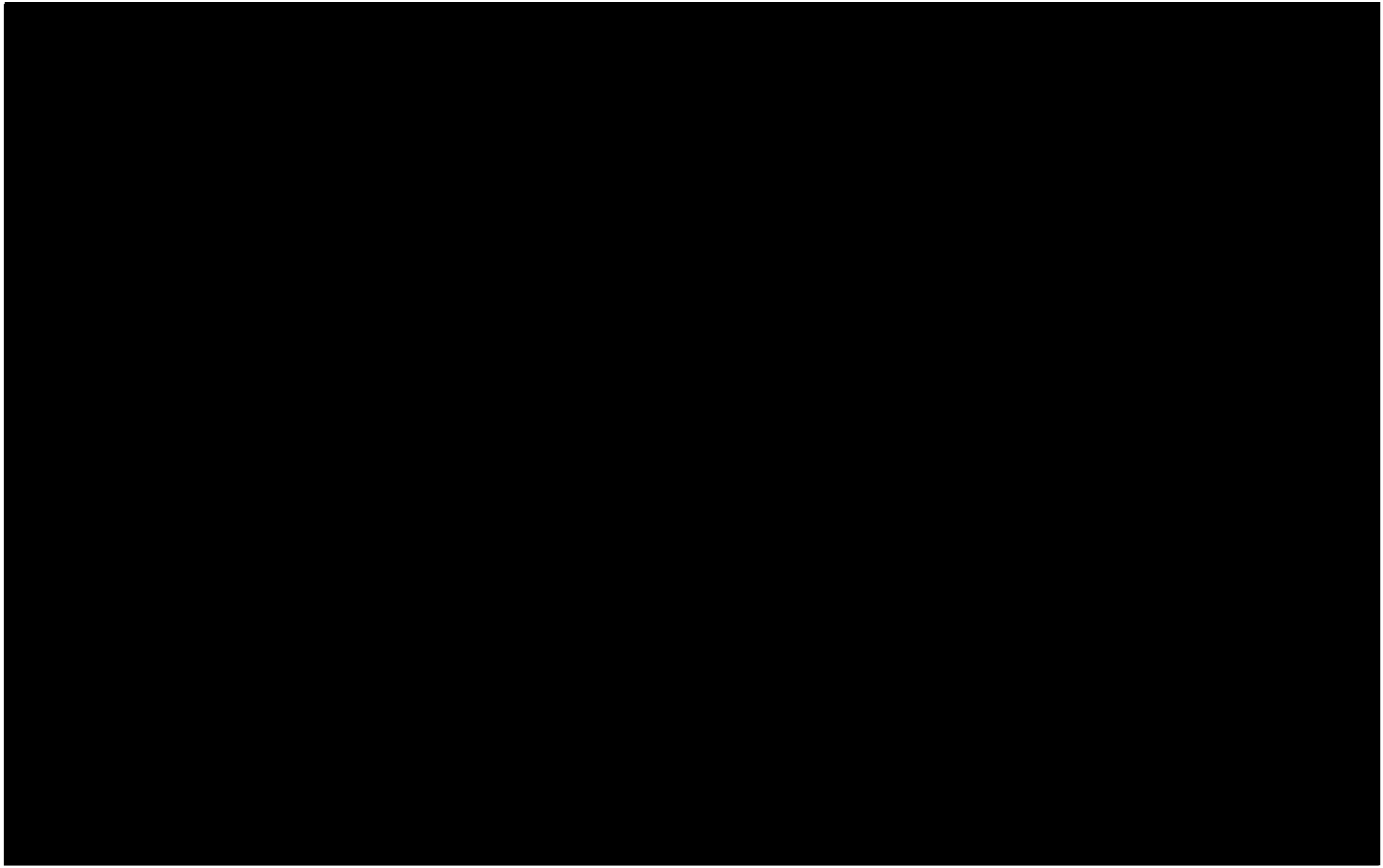
- Full Physical examination
- Vital signs supine for 5 minutes (heart rate, blood pressure, respiration rate and body temperature)
- Weight
- Adverse events
- Concomitant medication
- EULAR and ACR Response
- Visual Analog Scale (VAS) experience of pain (patient) and General Health
- VAS Rheumatoid Arthritis (RA activity patient's and Investigator's evaluation)
- Tender joint counts
- Swollen joint counts
- DAS28
- SF-36 and HAQ

- Health Economics Questionnaire *(Appendix 14.4)*
- Extensive laboratory:
  - Hematology: Hgb, HCT, RBC, WBC, differential count, platelet count, ESR
  - Chemistry: Sodium, potassium, chloride, total bilirubin, ALP, ALT (SGPT), AST (SGOT), gamma GT (GGT), LDH, CRP, CK, BUN, creatinine, glucose, uric acid, calcium (Ca++), phosphorous, total protein, albumin, HbA1C, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, osteocalcin and serum cortisol
  - Urinalysis: Glucose, N-telopeptide and creatinine
- ECG
- Urine pregnancy test (as applicable)
- For early termination visit, record the reason why the subject is terminating the study prematurely on the Case Report Form (CRF) and in the source documentation.

If the infusion is stopped or infusion rate is changed at any other time than already prescribed in the infusion instructions in the protocol, a PK sample should be obtained ASAP after the unscheduled change in infusion rate.

These patients have an additional exclusion criterion (blood donation). The patients participating in the PK sub-study will be compensated for the time spent at site and for the additional blood collection. .

Detailed operational procedures as well as information with regard to parameters, analytes for this PK sub-study are described in the PK manual.



8.4 Drug accountability

The Sponsor will supply the clinical Investigator with the investigational product, and other clinical drug supplies as agreed upon for the timely completion of the clinical study described above.

The investigational products (Nanocort and Depo-Medrol, as well as the placebo dummies) will be delivered to the study pharmacy. Study pharmacists will be unblind. It will be the responsibility of the study pharmacist to prepare the individual treatments based on randomization, treatment group and dose. Preparation on site is required to ensure the study blind. The investigational products will be dispensed only under the restricted conditions defined in the present protocol. Drugs will be administered by blinded personnel only. Time (start and end time of infusion) and date of administration and initials of the person administering the drug will be documented.

The pharmacist will record and acknowledge receipt of all shipments of the investigational product and document the lot numbers and 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 administered 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 unblinded monitor will be responsible for verifying the Investigator's documentation on receipt, use and return of investigational products. The unblinded monitor will check drug accountability at sites on an ongoing basis from the start of the study. At the end of the study, it must be possible to reconcile delivery records with records of used and returned study treatments. An account of any discrepancies must be provided. The unblinded monitor will prepare a final report of the accountability of the investigational product for filing in the investigator file.

Nanocort should be stored between 2 and 8°C, protected from light and kept in an appropriate secure area (e.g., a locked cabinet). All other related material can be stored at room temperature or per manufacturer's instructions.

The Sponsor (or designee) can provide the framework for documenting study treatment accountability throughout the study. The Investigational site must maintain an accurate written record of the shipment, dispensing, and return of study treatments. And an accurate

record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

At the conclusion of the study and after inspection by the unblinded monitor the Investigator will return all drug containers, drug labels, and a copy of the completed drug accountability form to the monitor for transfer to the appropriate parties. Sites may destroy medications locally at an appropriate time point, if previously agreed with the Sponsor.

8.5 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The Investigator can decide to withdraw a subject from the study for urgent medical reasons.

Reasons for subjects to be withdrawn from the study include, but are not limited to;

- The subject withdraws consent.
- Violation of eligibility criteria (if the violation is detected prior to drug administration).
- At the Investigator's or MM's discretion to protect subject safety and well-being.
- Subjects may also be discontinued due to the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects safety, occurrence of AEs, intake of non-permitted concomitant medication that might affect safety or study assessments/objectives, etc.

Reasons for discontinuation will be recorded.

Once dosing is complete, subsequent violation of the protocol should not be considered grounds for withdrawal. All subjects treated should be followed up for safety evaluation, if at all possible. If withdrawn due to an AE, subjects must be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator is stabilized. In all cases, the date the subject is withdrawn from the study and the reason(s) for withdrawal must be recorded on the electronic case report form (eCRF).

In the case of incomplete drug administration, subjects should not be withdrawn from the study, but should undergo all planned follow-up visits.

If a subject is withdrawn from the study for any reason, the Investigator must make every effort to perform the evaluations described for the End of Study/Early Termination Visit at Day 85 (Week 12), as soon as possible but preferably within 30 Days after their last study drug administration. Subjects withdrawn because of adverse experiences will undergo a

physical examination and laboratory tests planned at the follow-up visit (if required). A follow-up of AEs will also be undertaken.

Replacement of individual subjects after withdrawal

No subjects will be replaced. If any of the subjects is withdrawn from the study, the reason for withdrawal will have to be recorded in the case report form (eCRF) for all withdrawn subjects.

8.6 Follow-up of subjects withdrawn from treatment

All subjects treated should be followed up for safety evaluation if at all possible. If withdrawn due to an AE, subjects must be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator and MM to have stabilized. In all cases, the date the subject is withdrawn from the study and the reason(s) for withdrawal must be recorded on the case report form (eCRF).

In the case of incomplete drug administration, subjects should not be withdrawn from the study, but should undergo all planned follow-up visits.

If a subject is withdrawn from the study for any reason, the Investigator must make every effort to perform the evaluations described for the End of Study/Early Termination Visit at Day 85 (Week 12), as soon as possible but preferably within 30 Days after their last study drug administration.

8.7 Premature termination of the study

The study may be discontinued at the discretion of the Principal Investigator, Sponsor, or Independent Ethics Committee (IEC) based on the occurrence of the following (but not limited to):

- AEs unknown to date with respect to their nature, severity, and duration;
- Increased frequency and/or severity and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in recruitment;
- Cancellation of drug development;
- Notification by regulatory authorities

The written information concerning premature termination of the study will be provided to applicable recipients, such as Investigators, Sponsor or IECs.

9. SAFETY REPORTING

9.1 Disadvantageous event

In accordance to applicable legislation and guidelines, the Investigator will inform the subjects and the reviewing accredited ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited ethical committee, except insofar as suspension would jeopardise the subject's health. The Investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence in a subject who has received study drug, or any untoward or unintended response to an experimental intervention which does not necessarily have a causal relationship with the treatment. Adverse Events include:

- Any new undesirable medical experience or an unfavourable and unintended change of an existing condition that occurs during or after treatment.
- Untoward clinically significant manifestations of laboratory abnormalities (e.g., clinical chemistry, haematology, urinalysis, etc.) or other abnormal assessments (e.g., electrocardiogram, vital signs) independent of the underlying medical condition. If possible, abnormal laboratory findings with these characteristics should be reported as a clinical diagnosis rather than the abnormal value itself (e.g., "anemia" rather than "decreased blood count").

Situations where an untoward medical occurrence has not occurred (e.g., hospitalisation for elective surgery, social and/or convenience admissions) do not represent AEs.

Subjects will be carefully monitored throughout the study for AEs. At each study visit, subjects will be asked to report any AE. All AEs are followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted. The investigator will use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

Each collected AE, regardless of the relationship to study drug, will be recorded in the AE eCRF. All entries should contain an event term, date of onset, date of resolution, severity, action taken, outcome, relationship to study drug, and a seriousness assessment. The investigator will document all AEs in the subject's source document.

Severity will be assessed by Investigator according to the following definitions:

Mild: The event is of little concern to the subject and/or of no clinical significance. The event is not expected to have any effect on the subject's health or wellbeing.

Moderate: The subject experienced discomfort enough to cause interference with usual activity, and/or the condition required specific treatment. The event is of some concern to the subject's health or wellbeing. The event may require medical intervention.

Severe: The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or wellbeing. The event is likely to require medical intervention and/or close follow-up.

Life-threatening: The subject is at risk of death due to the adverse event as it occurred. This does not refer to an event that hypothetically might have caused death if it were more severe.

Death: Death related to adverse event.

Action taken is categorized as "none", "study drug discontinued", "study drug discontinued and restarted", "dose modified", "required concomitant medication", "required procedure", or "other".

Event outcome at resolution, or time last follow-up was recorded is categorized as: "event resolved"; "resolved with sequelae"; "ongoing"; "lost to follow-up"; or "death".

The investigator will determine the relationship of the event to the study drug according to the following criteria:

- **Not related:** The event was most likely caused by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs, and did not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration made a causal relationship unlikely.
- **Unlikely**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

- **Possibly related:** The event followed a reasonable temporal sequence from the time of drug administration, and/or followed a known response pattern to the study drug, but could have been produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs.
- **Probably related:** The event followed a reasonable temporal sequence from the time of drug administration, and/or followed a known response pattern to the study drug, and could not be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness or concomitant drugs.
- **Related:** The event follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether an AE is serious in other instances, such as an important medical event that may not be immediately life-threatening or resulting in death, or a hospitalisation that may jeopardize the subject or require intervention to prevent one of the above outcomes.

All serious adverse events will be reported by the investigator to the **Accelovance Pharmacovigilance (PV) within 24 hours** of first knowledge of the Investigator via the **Fax:** [redacted] All SAEs will be reported by submitting a completed SAE Report Form. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. It is critical that the information provided on the Sponsor's SAE Report Form matches the information recorded in AE eCRF

for the same event. In addition, the same information is to be recorded in the source documents.

The Investigator must also notify the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) in writing as soon as is practical, but at least within 15 Days after the Investigator has first knowledge of the serious adverse events.

Accelovance PV will notify Sponsor of all SAE's within 24 hrs of its initial receipt.

The Council for International Organizations of Medical Sciences (CIOMS) Form prepared by Accelovance PV will be shared with Sponsor for review and approval.

Pregnancy test will be performed at screening and at visits specified in the protocol. Subjects with a positive test at screening or during the study period will be excluded from the study. Women of child-bearing potential will be instructed to practice an acceptable method of birth control for the duration of the study. However, if subject becomes pregnant during the study, pregnancy will be recorded as a significant medical event and reported per SAE reporting procedure. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the pregnancy should be reported. Subjects who become pregnant during the study will be asked to discontinue the study drug if this can be done safely.

SAEs that result in death or are life threatening should be reported expeditedly. The expedited reporting will occur not later than 7 Days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 Days for completion of the report.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an IMP related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

- Summary of Product Characteristics (SPC) for an authorised medicinal product;
- Investigator's Brochure for an unauthorised medicinal product.

The time frame for submitting suspected, unexpected serious adverse drug reaction or other information which qualifies for reporting to European Medicines Agency (EMA) and all participating investigators is no later than 15 calendar days after initial receipt of the information by Accelovance PV.

Suspected and Unexpected fatal or life-threatening adverse reactions represent especially important safety information and, therefore, must be reported more rapidly to EMA. The requirement for reporting any Suspected and Unexpected fatal or life-threatening adverse reaction to EMA is no later than 7 calendar days after initial receipt of the information by Accelovance PV. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.

Accelovance PV will report any suspected unexpected serious adverse reactions (SUSARs) on behalf of the Sponsor to the IEC/CA according to local requirements.

The IRB/IEC should receive the following SUSARs expeditedly:

- SUSARs that have arisen in the clinical trial that was assessed by the IEC
- SUSARs that have arisen in other clinical trials of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the IEC

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the IEC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

Premature unblinding of study drug may occur to reveal whether a subject has been treated with Nanocort or Depo-Medrol®, Unblinding should occur only in an emergency and if the information is considered by the Investigator (or other treating physician) as medically necessary. If unblinding occurs prior to notification of the Medical Monitor the circumstances leading to the unblinding must be clearly documented and promptly reported by telephone or in writing to the Medical Monitor.

Development Safety Update Report

In addition to the expedited reporting of SUSARs, Accelovance Pharmacovigilance will submit, once a year throughout the clinical trial, a safety report to the accredited ethical committee competent authority, and competent authorities of the concerned Member States. This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study.

9.4 Data Safety Monitoring Board (DSMB) / Safety Committee

DSMB is not planned for this study. Nanocort contains prednisolone. Prednisolone is in clinical use for years. The reference product, Depo-Medrol, which contains methylprednisolone, is also clinically used in current practice for the treatment of a variety of diseases. Considering the known safety profile of prednisolone or methylprednisolone in clinical use, DSMB is not planned.

10. STATISTICAL ANALYSIS

10.1 General

Descriptive statistics, including the number and percentage for categorical variables, and the number, mean, standard deviation (SD), median, minimum and maximum for continuous variables will be provided. Listings of individual subjects' data will be produced. Where appropriate time trends will be shown by graphically displays.

For continuous data, one-way Analysis of variance (ANOVA) (in case of normally distributed variables) or the non-parametric Kruskal-Wallis test will be used; for categorical data and binary data the Chi-square test or Fisher's exact test will be used.

A detailed Statistical Analysis Plan (SAP) will be written and finalized in advance of database lock. All the details necessary to complete the statistical analyses will be provided in the SAP. This SAP should be approved by the Sponsor and MM (or designee) prior to un-blinding.

The statistical package SAS® v9.3 or higher will be used to produce all summary tables and data listings and to perform the hypotheses testing.

10.2 Primary study parameter

EULAR responders (good and moderate combined) at Day 8

EULAR responders (good and moderate combined) at Day 8 will be summarized by treatment group and pair-wise compared between both Nanocort arms and the Depo-Medrol arm using the Cochrane-Mantel-Haenszel test stratified by study site.

As sensitivity analysis a logistic regression model will be fitted on the EULAR responders with the stratification factor study site and additional baseline variables as covariates.. Proportional odds ratios will be presented. The SAP will specify the planned additional covariates .

10.3 Key Secondary parameters

EULAR good responder at Day 8,

EULAR responder (good and moderate combined) at Day 15

EULAR good responder at Day 15.

The key secondary parameters will be analyzed as the primary study parameter EULAR responder at Day 8.

10.4 Secondary study parameters

10.4.1 EULAR Response

EULAR response (good, moderate, no response) at Week 1, 2, 3, 4, 6, 8, and 12

EULAR responses will be summarized by treatment group and the treatment groups will be compared by using the non-parametric Wilcoxon-Mann-Whitney test. .

10.4.2 DAS28 mean and % change

Absolute and % change from Baseline in DAS28 scores at 1, 2, 3, 4, 6, 8 and 12 Weeks will be submitted to an analysis of covariance, including baseline scores and study site as covariates or to an appropriate non-parametric alternative (e.g., Kruskal Wallis test). The time course of DAS28 scores will be submitted to a repeated measures analysis of variance.

10.4.3 Time to first EULAR response (moderate or good)

Time to first EULAR response, will be analyzed using the Kaplan-Meier method; comparison between treatment groups will be performed using the log-rank test.

10.4.4 ACR 20/50/70 response scores

The comparison of ACR20, ACR50 and ACR70 response rates among treatment groups will be analyzed using a stratified Cochrane-Mantel-Haenszel test, .

10.4.5 Tender and swollen joint counts

The DAS28 score and the EULAR Response incorporate the tender and swollen joint counts. For this reason, no formal testing will be done between the three treatment groups. Descriptive statistics will be presented for the tender and swollen joint counts by treatment group.

10.4.6 Visual Analog Score (VAS)

- Patient VAS value for experience of pain and patient VAS value for General Health
- Patient and Investigator VAS value for RA activity

Changes from Baseline in VAS scores at 1, 2, 3, 4, 6, 8 and 12 Weeks, will be submitted to an analysis of covariance, including Baseline VAS scores and study site as covariates or to an appropriate non-parametric alternative (e.g., Kruskal Wallis test).

10.4.7 Quality of Life and RA activity questionnaires

Short Form 36 (SF-36) to assess physical and mental component at Baseline and Week 1, 2, 4, 6, and 12. Pair-wise comparisons of absolute changes from Baseline at Weeks 4, 6 and 12 will be performed using Analysis of covariance (ANCOVA), with study site, SF-36 score at Baseline DAS28 level, age and gender as covariates.

The Health Assessment Questionnaire (HAQ) at every visit (except Screening visit). Pair-wise group comparisons of HAQ score changes from Baseline at Weeks 3, 6 and 12 will be analyzed by ANCOVA, with study site, Baseline DAS28 level and HAQ score at baseline as covariates.

The Functional Assessment of Chronic Illness Therapy (FACIT) at Baseline, Week 4 and 6. The pair-wise comparisons between treatment groups of the changes from Baseline in FACIT-Fatigue scores will be performed by using ANCOVA with study site, Baseline DAS28 level and Baseline FACIT score as covariates.

For the ANCOVA analyses, least squares means and the pairwise comparisons between treatment groups in adjusted least-squares means with their Tukey 95% CIs will be presented.

Descriptive statistics for the surveys /questionnaires will be presented.

10.4.8 Maintenance of Improvement at 12 Weeks

Maintenance of Improvement at 12 Weeks will be compared between treatment groups using a stratified Cochrane-Mantel-Haenszel test.

10.4.9 Safety assessments

Safety results (AEs, vital signs, physical examinations, laboratory, ECG) will be compared between the Nanocort arms and the Depo-Medrol arm. Shift tables and shift plots will be used to evaluate changes in clinical laboratory test results at different time points compared to Baseline values. Proportion of patients whose test values are outside specific ranges will also be presented.

All abnormalities in physical examination, ECG and vital signs will be presented.

10.5 PK analysis

The PK subset of the study is exploratory and only descriptive PK parameters will be derived. PK analytes including free prednisolone and prednisolone phosphate will be assessed. Statistical comparison for PK parameters will not be done.

10.6 Other study parameters

No formal hypothesis testing of safety data will be undertaken; however, the data summaries will be examined for any trends amongst the dose levels.

10.7 Interim analysis

There will not be an interim analysis for this study.

10.8 Analysis Populations

The following analysis populations will be defined:

Intent to treat (ITT) population

All subjects randomized will be included in the ITT population, if:

- At least one dose of study medication was administered

Subjects will be assigned to treatment groups as randomized for analysis purposes.

Per protocol (PP) population

The per-protocol population will be defined as the subset of the ITT population without the following exclusions:

- Major violation of inclusion or exclusion criteria
- Withdrawal from the study before week 2
- Other major protocol violations, such as use of prohibited medication

Details will be described in the data review plan. Subjects will be assigned to treatment groups as treated for analysis purposes.

Safety (SAF) population

All subjects randomized will be included in the SAF population, if:

- At least one dose of study medication was administered and
- At least one post randomization safety assessment was performed.

Subjects will be assigned to treatment groups as treated for analysis purposes.

Since the primary endpoint is EULAR response on Day 8, those subjects who had received the first dose on Day1 and EULAR response is assessed will be considered for primary endpoint analysis as these patients are fulfilling the requirement for primary endpoint assessment. Secondary endpoints are also assessed depending on the dataset available by which the particular endpoint can be calculated.

A list of protocol violations leading to exclusion from the PP population will be finalized before database lock. During the blind data review before database lock the PP population will be defined.

10.9 Missing Data

The handling of missing data for the clinical endpoints will be discussed in detail in the SAP.

For the primary endpoint EULAR response on Day 8, subjects who withdraw from the study before Day 8, because of insufficient efficacy will be considered as non-responders.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study is to be conducted in compliance with the protocol and in accordance with International Conference of Harmonisation (ICH) guidances, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, the European Clinical Trial Directive 2001/20/EC of 4 Apr 2001 and European Clinical Trial Directive 2005/28/EC of 8 Apr 2005 and local ethical and legal requirements.

11.2 Recruitment and consent

Subjects will be recruited from the investigational sites based on the eligibility criteria provided in the protocol.

Voluntary written Informed Consent Form (ICF) must be obtained from each subject prior to performing any study related procedures in compliance with the recommendations of the Declaration of Helsinki. Subject should not be screened or study drug administered until the subject has signed an approved ICF written in a language that is understandable to the subject.

Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The ICF should be signed and personally dated in two originals by the subject and the person who conducted the informed consent discussion. The Investigator, or the attending health care professional, will explain the nature, purpose and risks of the study. The subject will be informed that he/she has the right to withdraw at any time from the study, without giving reasons. In this condition, the subject will also be informed that he/she will not receive any indemnity. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study.

Each subject should receive one original of the signed and dated written ICF and any other information provided to the subject. The second original of the signed and dated ICF should be retained in the Investigator's file. The Investigator should maintain a log of all subjects who sign the ICF.

11.3 Objection by minors or incapacitated subjects (if applicable)

No minors or incompetent adults will be enrolled in this study.

11.4 Compensation for injury

The Sponsor has a liability insurance which is in accordance with relevant legislation.

In the event of any suffering, deterioration in health or well-being or any harmful susceptibility or toxicity caused to subjects' participation in the trial, the subject will receive appropriate compensation irrespective of the question of legal liability.

The Sponsor has an insurance which is in accordance with the legal requirements in the participating countries. This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.5 Incentives

In addition to compensation for travel costs, a financial compensation will be provided to the subjects completing Baseline and Week 2 visits as compensation for the additional burden as per local regulations.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

12.1.1 Data Handling

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. With the subject's permission, medical information may be given to his personal physician or other appropriate medical personnel responsible for his/her welfare. Data generated by this study must be available for inspection by representatives of, other national and local health authorities, the Sponsor, and the IRB/IEC for each study site, if appropriate.

Subjects will be identified on CRFs and other documents submitted to the Sponsor or organisations working on behalf of the Sponsor by their subject number, or birth date, not by name or initials. Documents not to be submitted to the Sponsor or organisations working on behalf of the Sponsor that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

12.1.2 Data Coding

All subjects who sign a study informed consent will be assigned a unique subject identification number at the time of their Screening visit (after consent). Subjects will be identified by this unique subject identification number for the duration of their participation in the study.

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and subject names to enable records to be found at a later date. Subjects will be assigned identification numbers automatically via the eCRF.

12.1.3 Data Confidentiality

The Investigator is required to ensure that any documents or data given to the Sponsor or its representatives do not contain information that would affect the anonymity of the subjects.

The Investigator will obtain permission for direct access to subject data from the subject as part of the written informed consent procedure. This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the trial. Any party (e.g., domestic and foreign regulatory authorities, Sponsor personnel or its representatives, and auditors) with direct access must take all reasonable precautions, within the constraints of the applicable regulatory requirement(s), to maintain the confidentiality of the subject's identity and Sponsor's proprietary information.

12.1.4 Data Storage

Each research site will retain copies/originals of the approved trial or study protocol, subjects' participation agreements, relevant source documents and all other supporting documentation related to the trial or study for a period of fifteen (15) years. These documents should be retained for a longer (or shorter) period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will provide each Investigator with information concerning the current status of the investigational drug as this may relate to the above stated obligation for the retention of study records. The Sponsor will inform each study site as to when these documents no longer need to be retained. Study sites should contact the Sponsor prior to disposing of or archiving any such records.

12.2 Monitoring and Quality Assurance

The Sponsor has ethical, legal and scientific obligations to conduct this study in accordance with established research principles and the ICH/GCP guidelines. The Sponsor's representative has been delegated the responsibility for monitoring the conduct of the study in accordance with ICH/GCP. The Investigator must provide the monitor with full access to all source, medical and study documents as required for the study.

The monitor assigned to each research site is responsible for establishing the schedule and procedures to be followed for monitoring this study. The major function of the clinical monitor is consistent with the ICH GCP Guidelines to ensure; the rights and well-being of human subjects are protected, the reported trial data are accurate, complete and verifiable from source documents and that the conduct of the trial is in compliance with the currently approved protocol, and local regulations. The monitoring organization will be provided with appropriate training regarding the study IMP under investigation and will operate under written procedures to ensure compliance with the protocol.

On-site monitoring visits include a pre-study visit, periodic visits, and a final visit at the close of the study. The pre-study visit is intended to review the Investigational Plan with the investigator and to ensure that the investigator:

- has appropriate training, facilities, patient load, time, and willingness to comply with study requirements;
- has the approval of the supervising Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the Investigational Plan;
- has all study documentation and required records on site;

- and assumes responsibility for the investigation at her/his center.

Periodic visits are intended to assess investigator's adherence to the Investigational Plan, maintenance of records, reports and investigational products, and review of source documents for accuracy, completeness, and legibility. During these periodic visits, the monitor is required to assess the progress of the study toward meeting study objectives, and to identify any concerns that stem from observations of the review of the Investigator's patient records, study management documents, and informed consent documents, and to ensure accountability of all patients that have been tested under the study. The monitor's final on-site visit at completion of the study is intended to assure that all of the data have been properly completed, and to conduct a closing meeting with the investigator and her/his staff members.

Reports of the on-site visits will be made by the monitor and should include resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and any necessary corrective actions. At the close of the study, a final monitoring report will be prepared by the monitor.

Communications by telephone, facsimile (fax) or mail (or email) may be used as needed to supplement site visits. Prior to the beginning of this study, each Investigator will be informed as to the anticipated frequency of the monitoring visits. In addition, the research site will receive reasonable notification prior to each monitoring visit during the course of the study. Principles of Risk-based monitoring will be employed for this study.

At each visit, the Investigator will be expected to cooperate with Sponsor representative(s) for the review and verification of all CRFs, the drug supply and inventory records and any additional records as may have been previously arranged.

12.3 Amendments

The Investigator and research team must comply with ICH E6 principles and all applicable local regulatory laws and regulations. This protocol is to be followed exactly. To alter the protocol, amendments must be written, be agreed to by both the Sponsor and the Investigator, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

The IRB/IEC/Competent Authorities which granted original approval for the study must be notified of all changes in the protocol and must provide documented approval for any change or deviation which may increase the risk to the subject and/or which may adversely affect the

rights of the subject or validity of the investigation. This stipulation does not apply to those changes made to reduce discomfort of or risk to subjects.

A 'substantial amendment' is defined as an amendment to the terms of the IEC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the IEC and to the Competent Authority.

Non-substantial amendments will not be notified to the accredited IEC and the Competent Authority, but will be recorded and filed by the Sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.

All amendments will be distributed to all protocol recipients, with appropriate instructions.

12.4 Annual progress report

The Sponsor/Investigator will submit a summary of the progress of the trial to the accredited IRB/IEC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The Sponsor will notify the accredited IRB/IEC and the Competent Authority of the end of the study within a period of 90 Days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the Sponsor will notify the accredited IEC and the Competent Authority within 15 Days, including the reasons for the premature termination.

Within one year after the end of the study, the Investigator/Sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited IEC and the Competent Authority.

12.6 Public disclosure and publication policy

The final report will be written in English in a Word format and its structure will follow a template based upon the ICH E3[(i)] guidelines unless otherwise specified by the Sponsor during financial agreement.

Suggested inclusions in the report are: study objectives, materials and methods (including any deviations from the study protocol), evaluation of the study results, observations by the Investigator as to the value of the study drug per se, and a discussion of all adverse experiences with interpretation by the Investigator as to the study drug involvement.

All information concerning the tested drug and the Sponsor's operation, such as patent applications, formulae, manufacturing processes, basic scientific data and formulation information supplied by the Sponsor and not previously published are considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without written consent from the Sponsor.

It is understood by the Investigator that the information from the clinical study will be used by the Sponsor in connection with the development of the tested drug and, therefore, may be disclosed as required to other clinical Investigators or to government agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study.

The trial drug and the information in this document and in any future information supplied contain trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

Publication rules will be consistent with local regulation and will be addressed in the study contract and should not be in contradiction with the text in the protocol.

13. REFERENCES

1. Bodman KB, Roitt IM. The pathophysiology of rheumatoid arthritis. Fund Am Clin Immunol 1994; 2:73–81.
2. Guidelines for the management of rheumatoid arthritis: American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum 1996; 39:713–22.
3. Saag KG. Glucocorticoid use in rheumatoid arthritis. Curr Rheumatol Rep 2002; 4:218–25
4. Snell ES. The pharmacological properties of corticosteroids in relation to clinical efficacy. Br J Dermatol 1976; 94 SupPEG-lip PLP 12:15–23.
5. Nanocort Development Safety Update Report (DSUR) #4, 25 March 2015.
6. Aletaha, D., et al., 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism, 2010. 62(9): p. 2569-2581.
7. Sokka, T., M. Envalds, and T. Pincus, Treatment of rheumatoid arthritis: a global perspective on the use of antirheumatic drugs. Mod Rheumatol, 2008. 18(3): p. 228-39.
8. Singh, J.A., et al., 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease - modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken), 2012. 64(5): p. 625-639.
9. Smolen, J.S., et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis, 2010. 69(6): p. 964-75.
10. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187583.
11. Duru, N., et al., EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis, 2013. 72(12): p. 1905-13.
12. Hoes, J.N., et al., EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis, 2007. 66(12): p. 1560-7.
13. Dams ET, Oyen WJ, Boerman OC, Storm G, Laverman P, Kok PJ, Buijs WC, Bakker H, van der Meer JW, Corstens FH. 99mTc-PEG liposomes for the scintigraphic detection of infection and inflammation: clinical evaluation. J Nucl Med 2000; 41:622-630.

[redacted]

15. Metselaar, J.M., et al., Complete remission of experimental arthritis by joint targeting of glucocorticoids with long-circulating liposomes. Arthritis Rheum, 2003. 48(7): p. 2059-66.
16. Metselaar, J.M., et al., Liposomal targeting of glucocorticoids to synovial lining cells strongly increases therapeutic benefit in collagen type II arthritis. Ann Rheum Dis, 2004. 63(4): p. 348-53.

17. Nanocort Investigator's Brochure (IB) Edition 5.0, Release Date 17 July 2015.
18. http://www.rxlist.com/depo-medrol-drug.htm.
19. http://emupdates.com/wp-content/uploads/2009/11/ICUPocketGuide.pdf.
20. Wolfe F1, Michaud K, Pincus T., Development and validation of the health assessment questionnaire II: a revised version of the health assessment questionnaire. Arthritis Rheum. 2004 Oct;50(10):3296-305.
21. Ware JE Jr1, Sherbourne CD, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun; 30(6):473-83.
22. http://www.facit.org/FACITOrg/Questionnaires.
23. Felson DT1, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V, et al., American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis Arthritis Rheum. 1995 Jun; 38(6):727-35.

14 APPENDICES

14.1 SF-36

14.2 HAQ

14.3 FACIT

14.4 Health Economics Questionnaire

Note: Appendices are *samples only*; current versions will be used as appropriate.

STATISTICAL ANALYSIS PLAN

STUDY: CLR_15_05

A Phase III, Randomized, Double-Blind, Double Dummy, Active Controlled, Multi-Center Study to Evaluate the Efficacy and Safety of Intravenous Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) compared with intramuscular injection of methylprednisolone acetate in Subjects with Active Rheumatoid Arthritis

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Sponsor: Sun Pharma Global FZE
Office No. 43, Block-Y, SAIF Zone
PO Box No. 122304
Sharjah, United Arab Emirate

Author: [redacted]

Date: June 7, 2018

Version: V5.2

CLR_15_05 SAP

Sign-Off Signatures

Author: [redacted]

Peer Review:

Approved by:

Approved by: [redacted]

Approved by:

TABLE OF CONTENTS

List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood Urea Nitrogen
CA	Competent Authority
CK	Creatine kinase
Ca^{++}	Calcium
CRF	Case report form
CRP	C-reactive protein
DAS28	Disease Activity Score in 28 Joints
DMARDs	Disease-modifying antirheumatic drugs
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	The Functional Assessment of Chronic Illness Therapy
FWER	Family wise error rate
HAQ	Health Assessment Questionnaire
HEQ	Health Economics Questionnaire
HbA1c	Hemoglobin A1c
HCT	Hematocrit
HCV	Hepatitis C virus
HDL	High-density lipoprotein
Hgb	Hemoglobin
ICF	Informed Consent Form
ITT	Intent To Treat
IV	Intravenous
IWRS	Interactive Web-based Randomization System
K^{+}	Potassium
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MTX	Methotrexate
Na^{+}	Sodium
PE	Physical examination
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per protocol
QoL	Quality of Life
RA	Rheumatoid Arthritis

RBC	Red blood cells
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical analysis plan
SD	Standard deviation
SF-36	Short Form 36
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPC	Summary of Product Characteristics
VAS	Visual Analogue Scale
WBC	White blood cells

1. Introduction

This analysis plan gives a detailed description of the statistical methodologies, data listings, and summary tables planned in the analysis of the data in the CLR_15_05 study.
The statistical data analysis, described in this document, is intended to provide unbiased and valid conclusions concerning the objectives of the study.

1.1 Study Population

The study has been conducted at 21 sites in the Netherlands and Belgium. Sites were selected based on previous study experience in RA and accessibility to study required populations. The study population will consist of male and female subjects (≥ 18 years old) with active RA who are experiencing a flare / exacerbation defined as a recent increase in symptoms and a measured increase in DAS28 > 1.2 or > 0.6 if DAS28 ≥ 3.2 despite disease-modifying anti-rheumatic drugs (DMARDs) therapy or treatment naïve patients compared to last DAS28 measurement (maximum 6 months before screening).

1.2 Study Design

The study is a randomized, double- blind, double dummy, active controlled, parallel, multi-center study in which IV Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) will be compared with IM injection of methylprednisolone acetate (Depo-Medrol®) to evaluate efficacy and safety. Each patient will receive an infusion and an IM injection containing either an active treatment or a dummy treatment. Opaque IV lines, sleeved bags and opaque syringes will be used to maintain blinding of either liposomal product or reference product. The total duration of the trial is 14 weeks maximum for each subject (up to 2 weeks of screening period and 12 weeks of treatment with follow up).

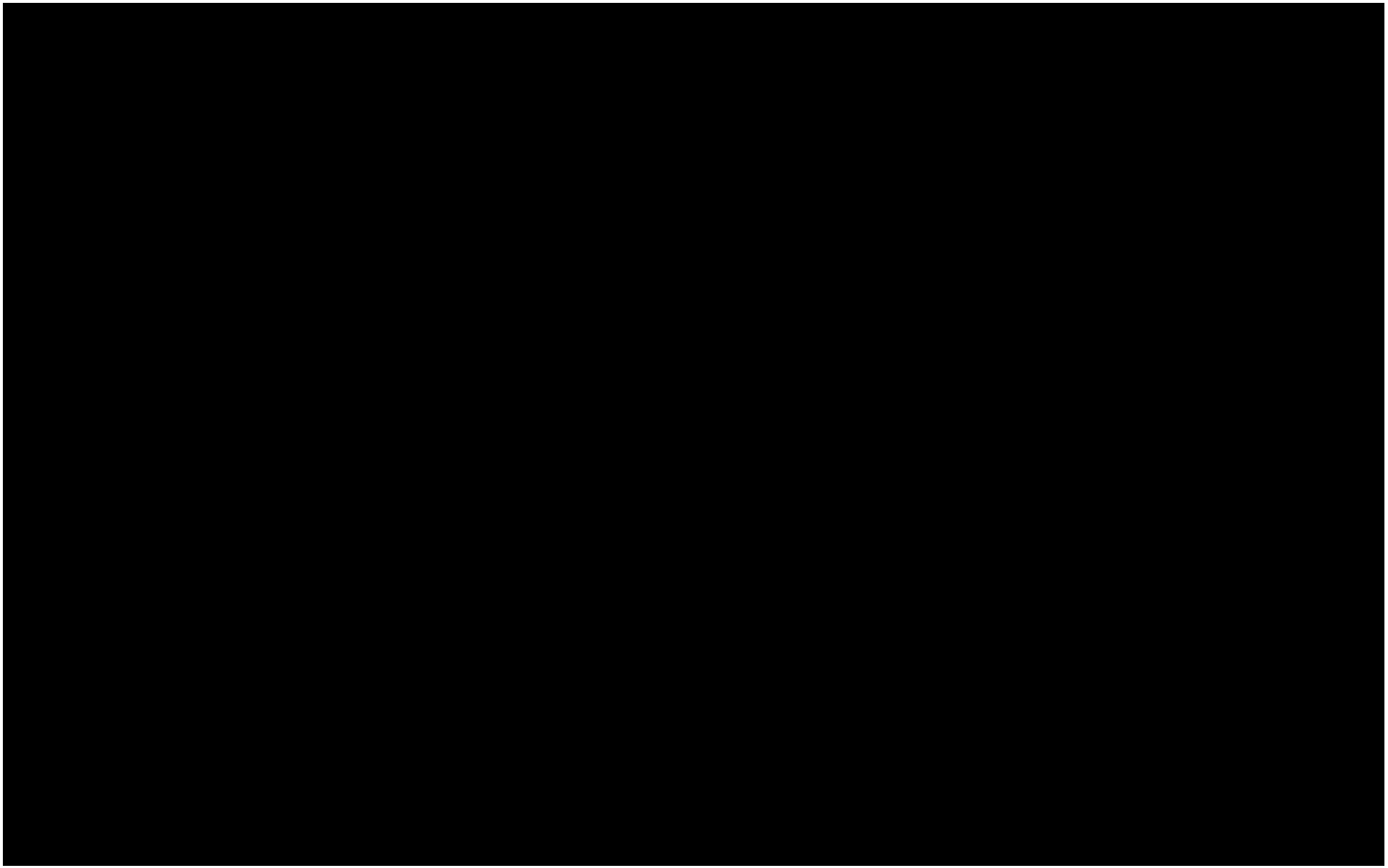
During this 14 weeks study, the dosage of any DMARDs should not be changed (in case the subject is receiving such treatment at screening). All subjects will be provided an informed consent form (ICF) containing information about the study. After fully understanding of the ICF, subjects will voluntarily sign the ICF. Subjects will enter a screening period for up to 14 Days to assess laboratory values and other inclusion/exclusion criteria. Medical history and serious medical conditions as determined by the Principal Investigator (PI) will be reviewed during screening. In addition, the screening period will include a

physical examination, blood and urine collection for laboratory assessments, vital signs, electrocardiogram (ECG) and confirmation of RA diagnosis (flare criteria).

Subjects with active RA who meet all eligibility criteria will undergo Baseline visit (Day 1) assessments. At this visit, prior to receiving treatments, subjects will be assessed for baseline parameters and then will be randomized. A total of up to 330 subjects will be enrolled and randomized into 3 groups indicated below:

- Nanocort 75 mg IV infusion and IM saline injection
- Nanocort 150 mg IV infusion and IM saline injection
- Depo-Medrol® 120 mg IM injection and IV saline infusion

Dosing will occur on Baseline (Day 1) and Week 2 (Day 15). Study visits will occur at Week 1, Week 2, Week 3, Week 4, Week 6, Week 8 and Week 12 / End of Study (EOS) to assess efficacy and safety evaluations as indicated in the Schedule of Assessments. Subjects receiving any treatment dose will be followed till Week 12 for safety if possible.



1.3 Primary and secondary study objectives

1.3.1 Primary Objectives

To assess efficacy and safety (treatment of signs and symptoms) of Nanocort in comparison to a standard of care medication (Depo-Medrol) in subjects with active rheumatoid arthritis who are experiencing a flare/exacerbation.

1.3.2 Secondary Objectives

- To evaluate patient-reported outcomes in subjects with Active Rheumatoid Arthritis who are experiencing a flare/exacerbation receiving IV Nanocort as compared with subjects receiving IM injections of Depo-Medrol.
- To assess PK parameters, in a subset population from each treatment group.

1.4 Primary, Key Secondary and Secondary Endpoints

1.4.1 Primary Endpoint

- The EULAR responder (moderate and good combined) rate at Week 1 (Day 8)

1.4.2 Key Secondary Endpoints

- The EULAR good responder (only good) rate at Week 1 (Day 8)
- The EULAR responder (moderate and good combined) rate at Week 2 (Day 15)
- The EULAR good responder (only good) rate at Week 2 (Day 15)

1.4.3 Secondary Endpoints

- EULAR response at Week 1 (Day 8), Week 2 (Day 15), Week 3, 4, 6, 8 and 12
- DAS28 mean and % change from baseline at Week 1, 2, 3, 4, 6, 8 and 12
- Time to first EULAR responder (moderate/good)
- ACR 20/50/70 response scores at Week 1, 2, 3, 4, 6, 8 and 12
- Tender joint counts at Week 1, 2, 3, 4, 6, 8 and 12
- Swollen joint counts at Week 1, 2, 3, 4, 6, 8 and 12
- Patient pain and Global Visual Analog Score (VAS) score at Week 1, 2, 3, 4, 6, 8 and 12
- Investigator Global Visual Analog Score (VAS) score at Week 1, 2, 3, 4, 6, 8 and 12

- Short Form 36 (SF-36) to assess physical and mental component at Week 1, 2, 4, 6 and 12
- Health Assessment Questionnaire (HAQ) at Week 1, 2, 3, 4, 6, 8 and 12.
- The Functional Assessment of Chronic Illness Therapy (FACIT) at Baseline, Week 4 and 6
- Health Economics Questionnaire at Week 12
- Maintenance of Improvement at 12 Weeks assessed during a blinded review by the Medical Monitor and PI at the end of the study, before database lock
- Pharmacokinetics (PK) assessment in subset of patient population at Baseline, Week 1, 2, 3, 4 and 6
- AEs (including glucocorticoid related AEs), AEs leading to withdrawal, AEs leading to discontinuation of medication, and AEs due to infusion reactions)
- Vital signs
- Physical examinations
- Laboratory
- ECG
- Assessment by monitoring cortisol levels at Screening, Baseline 6 and 12 - weeks

2. Analysis Populations

Analysis of safety data will be based on the safety population (SAF). The primary analysis population for efficacy will be the Intent-to-Treat (ITT) population. Analysis of primary efficacy endpoint and key secondary endpoints will also be performed on the Per-Protocol (PP) population to confirm the findings from the ITT population.

2.1 Intent-to-Treat Population

All patients randomized into the study will be included in the ITT population, if at least one dose or a part of Nanocort IV/Placebo infusion or Depo-Medrol/placebo IM injection was administered and at least one post-baseline efficacy measurement was performed.

Patients will be analyzed within the original treatment group they were randomized to. All analyses will be completed for the ITT population. The main analyses for assessment of study success will be analysis of the primary endpoint on the ITT population (see section 4.8).

2.2 Per-Protocol Population

The PP population is defined as a subset of the ITT population excluding major protocol violators. The following is a list of some of the conditions which, if met, would likely exclude the patient from the PP population:

- Violation of inclusion or exclusion criteria
- Breaking the blind
- Randomization irregularities
- Withdrawal from the study before week 12
- Current use of prohibited DMARDs or biological RA treatments per protocol
- Any other relevant violations observed during the conduct of the trial

Final specification of the criteria, definitions and processes are detailed in the 'Blinded Review Report of Deviations Leading to Exclusion from the Per-Protocol Analysis' document.

Patients will be analyzed based on the treatment received. Analyses on the PP population will be seen as supportive analyses. The primary and secondary efficacy endpoints will be analyzed for the PP population.

The list of protocol deviations leading to exclusion from the PP population will be finalized before database lock. During the blind data review before database lock the PP population will be defined by determining subjects not eligible for the PP population and the reason they cannot be included.

2.3 Pharmacokinetic Evaluable Population

This SAP describes only the analyses for the study objectives not involving the PK objectives. The PK objectives will be described in a separate analysis plan.

2.4 Safety Population

The safety population (SAF) will include all patients who receive at least one infusion or part of infusion with Nanocort/placebo or at least one IM injection or

part of IM injection with Depo-Medrol/placebo and had at least one post baseline safety assessment.

Patients will be assigned to treatment groups as treated for analysis.

3. Blinded Review of the Data

A blinded data review will be held before breaking the blind. The blinded data review will be performed by at least the Principal Investigator, the Medical Monitor, the Study Lead and the Trial Statistician**.** The goal of the blinded data review is to determine for each subject the maintenance of improvement at 12 Weeks, the protocol violations and to evaluate the impact of these protocol violations on the EULAR response.

The decisions taken during the blinded data review will be finalized and signed by participants on the blinded data review report before unblinding.

4. Statistical and Analytical Methods

This analysis plan gives a detailed description of the statistical methodologies, data listings, and summary tables planned in the analysis of the data in the CLR-15-05 study. This section describes the statistical analyses of the study based on the statistical section of the protocol (CLR15_05_Prot_V3.1_Amend_25Sep2017.pdf). Any difference with the protocol will be identified and documented. The statistical data analysis, described in this document, is intended to provide unbiased and valid conclusions concerning the objectives of the study.

This SAP describes only the analyses for the study objectives not involving the PK objectives. The PK objectives will be described in a separate analysis plan.

4.1 General Statistical Considerations

Individual data listings will be provided for all subjects enrolled, sorted by treatment group, site, subject and time point. Summary tables will be presented for the safety population by treatment group.

Descriptive statistics for continuous variables will be number of subjects (N), mean (Mean), standard deviation (SD), median (Median), minimum (Min) and maximum (Max). For categorical variables, the absolute (N) and relative frequency

(%) will be tabulated. Confidence intervals (CI) for mean values will be added if appropriate.

The analyses of the primary and key secondary efficacy endpoint are described in sections 4.8.1 and 4.8.2.

Due to early termination of the study, the sample size will be much less than planned. As a result, the statistical power can be inadequate for the planned gatekeeping methodology. Therefore, standard hypothesis testing methods may be used instead to analyze the data.

4.2 Missing Data Handling

Imputation will be implemented for partial start/end dates of adverse events dates. If the start day is missing, impute the 1st of the month, unless month and year are the same as month and year of the first dose of study drug then impute the first dose date. If start day and start month are both missing, impute 1st January but if year is the same as year of the first dose date, then impute first dose date. If the end day is missing, impute the last day of the month. If end day and end month are both missing impute 31st December. No other imputation of missing data will be performed, and only available data will be presented.

4.3 Baseline Definition

For all variables, baseline will be considered to be the last value obtained prior to first start of treatment, and may be on Screening or on Day 1, dependent on parameter. Change from baseline will be the difference between the value at a given time point and the baseline value.

4.4 Definition of Study Day and Visit Window

4.4.1 Study Day

For each patient, the day of first dose of study medication (Nanocort/placebo IV infusion and Depo-Medrol/placebo IM injection) administered on or after the day of randomization will be considered study day 1. Each assessment will be assigned a study day. The calculation for study day is dependent on whether the actual date of assessment is before or after the date of study day 1 and is calculated as follows:

Before study day 1: study day = (date of assessment – date of study day 1).

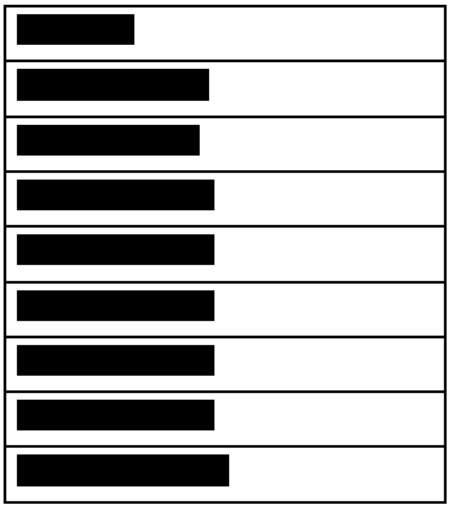
On or after study day 1: study day = (date of assessment – date of study day 1) +1.

If the full date of the assessment is not known or not imputable based on the guidelines in Section 4.2, then no study day will be assigned.

For each patient, the end of the study is defined as the date of their last contact in this study.

4.4.2 Visit Window

Data will be analyzed based on the categorized visit captured in the database. No dates will be used to reassign visits or define visit windows. The visits captured in the database include:



4.5 Patient Disposition

The number and percentage of subjects allocated to each of the populations will be summarized for all enrolled subjects. The number and percentage of subjects completing the study, discontinued, the reasons of discontinuation and the study duration (end of study date-date of first treatment +1) will be tabulated overall and by treatment.

4.6 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics, including date of birth, race, height, smoking history and Rheumatoid Factor (RF) will be summarized by treatment group and overall.

4.7 Medical and Surgical History

Numbers and percentages of subjects with any known history of relevant abnormalities, disease or surgery will be summarized by treatment group and overall. Reported term, preferred term, body system code, date of onset/procedure and date of resolution or ongoing will be listed.

Medical history will be coded by the MedDRA coding dictionary, version 19.

4.8 Efficacy Analysis

The primary and key secondary analyses will be completed for the ITT and PP populations.

Due to early termination of the study, the sample size will be much less than planned. As a result, the statistical power can be inadequate for the planned gatekeeping methodology. Therefore, standard hypothesis testing methods may be used instead to analyze the data.

To account for these possibilities and to facilitate better understanding of the data, the data will be analyzed 'as planned' in the protocol AND using more simple, unadjusted alpha analyses with basic chi-square tests. Therefore the data (Table 8A and 8B) will be analyzed two ways:

- Original Primary and Key Secondary Analyses using Hochberg's procedure and gatekeeping methods
- Modified Primary and Key Secondary Analyses using simple chi-square tests.

4.8.1 Original Analyses

4.8.1.1 Primary Analyses

The primary endpoint is EULAR response (good and moderate combined) rate at Day 8. The primary analysis involves two comparisons: 1) Nanocort 150 mg vs. Depo-Medrol®, 2) Nanocort 75 mg vs. Depo-Medrol®.

[redacted]

H0,1 : EULAR response (good and moderate combined) rate at Day 8 for Nanocort 150 mg - EULAR responder rate at Day 8 for Depo-Medrol® = 0

vs

H1,1 : EULAR response (good and moderate combined) rate at Day 8 for Nanocort 150 mg - EULAR responder rate at Day 8 for Depo-Medrol® ≠ 0

and

H0,2 : EULAR response (good and moderate combined) rate at Day 8 for Nanocort 75 mg - EULAR responder rate at Day 8 for Depo-Medrol® = 0

vs

H1,2 : EULAR response (good and moderate combined) rate at Day 8 for Nanocort 75 mg - EULAR responder rate at Day 8 for Depo-Medrol® ≠ 0

The primary analyses will be completed for the ITT and PP populations.

4.8.1.2 Key Secondary Analyses

The three key secondary endpoints are: 1) EULAR response (good) rate at Day 8, 2) EULAR response (good and moderate combined) rate at Day 15, and 3) EULAR response (good) rate at Day 15. Both comparisons (Nanocort 150 mg vs. Depo-Medrol®, and Nanocort 75 mg vs. Depo-Medrol®) will be completed for each of the three key secondary endpoints (i.e., up to 6 key secondary analyses).

The key secondary hypotheses will only be tested if at least one primary analysis is significant. If for one of the dosages the primary analyses is not significant, then the corresponding key secondary hypotheses will not be tested. The key secondary hypotheses will be tested with a two-sided confidence level, α_s. The calculation of α_s depends on the maximum p-value from the primary hypotheses, the significance of the primary hypotheses and $\alpha_{p.}$

Step 1: The primary hypotheses are tested using Hochberg procedure at $\alpha_p = 0.045 < \alpha$ (0.05). If at least one of the primary null hypotheses is rejected then go to Step 2. The significance value for Step 2 (α_s) is a function of largest primary p-value.

Step 2: Test the secondary null hypotheses using Hochberg procedure at α_s.

$\alpha_s = \min(\lambda \alpha^*/(p^*)^2, \alpha_p)$ if $p^* > \alpha_p$ and

$\alpha_s = \alpha$ if $p^* <= \alpha_p$

Where p* is the largest primary p-value, λ is chosen to control the global FWER at the alpha level.

$\alpha^* = \alpha_p(1\text{-sqrt}(2- \alpha_p/(k_1- 1) – \alpha / \alpha_p)^2$ if $\alpha' <= \alpha$

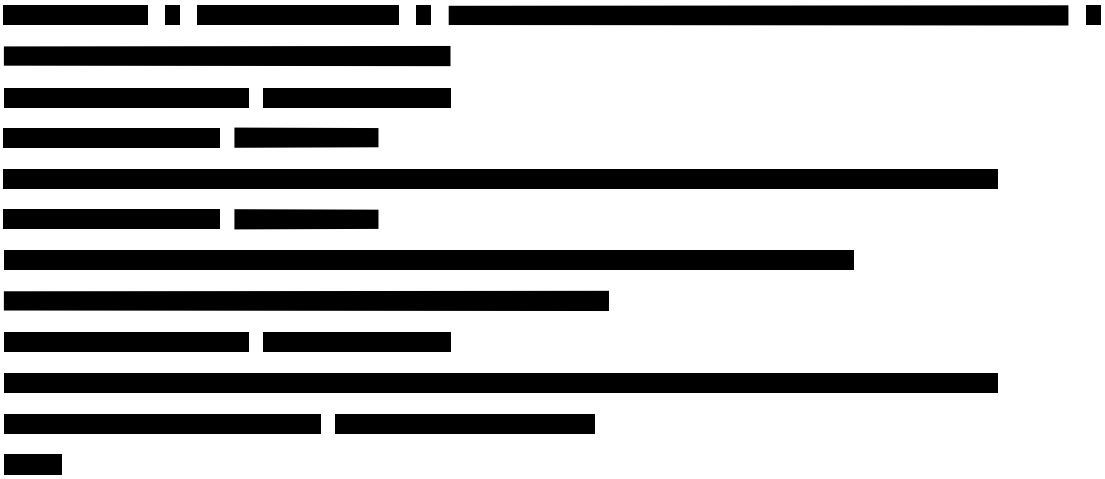
$= \alpha_p (\alpha - \alpha_p)/ (k_1 -1 - \alpha_p)$ if $\alpha' > \alpha$

Where $\alpha' = \alpha_p + \alpha_p^2/(k_1 – 1) - \alpha_p^3 /(k_1 – 1)^2$

K_1 = Number of primary endpoints (in this case k1 = 2)

The significance level carried over to α_s depends on the magnitude of the primary p-values rather than the number of significant primary p-values. This method assumes a full parametric model. The joint distribution of the hypotheses in primary and secondary endpoints is considered to calculate λ. If the joint distribution of the test statistic is not specified, the λ parameter is chosen under the worst-case scenario.

[redacted]



The key secondary analyses will be completed for the ITT and PP populations.

4.8.2 Simplified Analyses

The primary and key secondary analyses will be completed using the Hochberg and gatekeeping methodology described above but will also be analyzed using simple chi-square tests.

The simplified analyses will be completed for the ITT and PP populations.

4.8.3 Other Secondary Analyses

All other secondary analyses will be completed for both the ITT and PP populations. EULAR response (good, moderate, no response) at Week 1, 2, 3, 4, 6, 8 and 12 will be summarized by treatment group and the treatment groups will be compared by using the non-parametric Wilcoxon-Mann-Whitney test.

DAS28 will be summarized and analyzed at Week 1, 2, 3, 4, 6, 8 and 12. The DAS28 score is calculated as follows:

$$DAS28 = \left(0.555 \times \sqrt{TJC}\right) + \left(0.284 \times \sqrt{SJC}\right) + \left(0.7 \times \log_e ESR\right) + \left(0.0142 \times GH\right)$$

where TJC = tender joint counts on 28 joints, SJC = swollen joint counts on 28 joints, GH = general health, i.e. patient's global assessment of disease activity (100 mm VAS) and ESR = erythrocyte sedimentation rate (mm/hr). If ESR was not available, then CRP may be used instead. See Appendix C for details on scoring and coding. At a particular timepoint, if one or more of the four components used in calculating DAS28 are missing, then the DAS28 will be considered missing at that timepoint.

If DAS28 scores are approximately normally distributed via visual inspection, then DAS28 scores at 1, 2, 3, 4, 6, 8 and 12 weeks will be analyzed using analysis of covariance (ANCOVA), including baseline scores and study site as covariates. If DAS28 scores are markedly non-normally distributed via visual inspection, then the Kruskal-Wallis test will be used to compare the groups at each time point. In addition to the group comparison, the time course of DAS28 scores will be submitted to a repeated measures analysis of variance, with treatment group, time and the interaction of treatment group and time in the model.

If the percentage change in DAS28 scores is approximately normally distributed via visual inspection, then % change at 1, 2, 3, 4, 6, 8 and 12 weeks will be analyzed using ANCOVA, including baseline scores and study site as covariates. If % change is markedly non-normally distributed via visual inspection, then the Kruskal-Wallis test will be used to compare the groups at each time point. In addition to the group comparison, the time course of % change will be submitted to a repeated measures analysis of variance, with treatment group, time and the interaction of treatment group and time in the model.

Time to first EULAR response (moderate or good) will be analyzed using the Kaplan-Meier method; comparison between the treatment groups will be performed using the log-rank test.

American College of Rheumatology (ACR) 20/50/70 response ~~a~~t week 1, 2, 3, 4, 6, 8 and 12 will be summarized and analyzed. See Appendix D for details on scoring and coding. ACR score is a scale to measure change in rheumatoid arthritis symptoms. It is named after the American College of Rheumatology. Different degrees of improvement are referred to as ACR20, ACR50, ACR70. The following definition of improvement was selected: 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant [23]. ACR 50 and ACR 70 criteria are defined in a manner similar to that for ACR 20, but with improvement of at least 50 percent and 70 percent in the individual measures, respectively. The comparison of ACR20,

ACR50 and ACR70 response rates among treatment groups will be analyzed using a stratified Cochrane-Mantel-Haenszel test.

Tender and swollen joint counts at week 1, 2, 3, 4, 6, 8 and 12 will be summarized. The DAS28 score and the EULAR Response incorporate the tender and swollen joint counts. For this reason, no formal testing will be done between the three treatment groups.

Four Visual Analog Scores (VAS) will be summarized and analyzed at week 1, 2, 3, 4, 6, 8 and 12 including: 1) patient VAS value for experience of pain, 2) patient VAS value for General Health, 3) patient VAS value for RA activity, and 4) investigator VAS value for RA activity.

If the change from baseline in VAS is approximately normally distributed via visual inspection, then the change from baseline in VAS at 1, 2, 3, 4, 6, 8 and 12 weeks will be analyzed using ANCOVA, including baseline scores and study site as covariates. If the change from baseline in VAS is markedly non-normally distributed via visual inspection, then the Kruskal-Wallis test will be used to compare the groups at each time point.

Short Form 36 (SF-36) to assess physical and mental component at baseline, week 1, 2, 4, 6, and 12 will be summarized and analyzed. See Appendix A for details on scoring and coding. If the change from baseline is approximately normally distributed via visual inspection, then the change from baseline at 1, 2, 3, 4, 6, 8 and 12 weeks will be analyzed using ANCOVA, including baseline scores, age and gender as covariates. If the change from baseline is markedly non-normally distributed via visual inspection, then the Kruskal-Wallis test will be used to compare the groups at each time point.

Health Assessment Questionnaire (HAQ) at baseline, week 1, 2, 3, 4, 6, 8 and 12 will be summarized and analyzed. See Appendix E for details on scoring and coding. If the change from baseline is approximately normally distributed via visual inspection, then the change from baseline at 1, 2, 3, 4, 6, 8 and 12 weeks will be analyzed using ANCOVA, including baseline HAQ, baseline DAS28 and study site as covariates. If the change from baseline is markedly non-normally distributed via

visual inspection, then the Kruskal-Wallis test will be used to compare the groups at each time point.

FACIT Fatigue Scale at baseline, week 4 and 6 will be summarized and analyzed. See Appendix F for details on scoring and coding. If the change from baseline is approximately normally distributed via visual inspection, then the change from baseline at 1, 2, 3, 4, 6, 8 and 12 weeks will be analyzed using ANCOVA, including baseline FACIT, baseline DAS28 and study site as covariates. If the change from baseline is markedly non-normally distributed via visual inspection, then the Kruskal-Wallis test will be used to compare the groups at each time point.

Maintenance of Improvement at 12 Weeks assessed during a blinded review by the Medical Monitor (MM) and Principal Investigator (PI) at the end of the study will be compared between treatment groups using a stratified Cochrane-Mantel-Haenszel test, stratified by study site.

The Health Economics Questionnaire (HEQ) at week 12 will be summarized in a table of the responses for each treatment group as recorded on the questionnaire.

4.9 Safety Analyses

Safety results (AEs, vital signs, physical examinations, laboratory, ECG) will be compared between the Nanocort arms and the Depo-Medrol arm. Shift tables and shift plots will be used to evaluate changes in clinical laboratory test results at different time points compared to Baseline values. Proportion of patients whose test values are outside specific ranges will also be presented. All abnormalities in physical examination, ECG and vital signs will be presented.

No formal hypothesis testing of safety data will be undertaken; however, the data summaries will be examined for any trends amongst the dose levels.

4.9.1 Laboratory Results

Hematology, chemistry and urinalysis analysis test results in SI units will be summarized by lab test, treatment group and time point. For hematology, chemistry and urinalysis tests, changes from baseline will be included in these tables.

Abnormality findings i.e. normal, abnormal, not clinically significant (NCS) or abnormal, clinically significant (CS) will be summarized by lab test, treatment group and time point.

Shift tables will be provided for each lab test with baseline value (low, normal, high) for each treatment group across the top and the time point value (low, normal, high) along the side.

4.9.2 Vital Signs

Vital sign results and absolute changes from baseline for systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and body temperature will be summarized by treatment group and time points.

4.9.3 Physical Examinations

The complete and abbreviated physical examination results will be tabulated by treatment group and time points. The number and percentage of subjects with normal, abnormal, not clinically significant and abnormal, clinically significant results will be given.

4.9.4 ECG

The number and percentage of subjects with clinically significant results will be summarized by treatment group and time point.

4.9.5 Concomitant Medications

The number and percentage of subjects with *at least* one concomitant medication (CM) and one CM given for AE will be tabulated by treatment and overall. Concomitant medication will be coded by the WHODD coding dictionary version June 2015.

4.9.6 Adverse Events

The number and percentages of subjects with different AEs will be tabulated with MedDRA System Organ Class (SOC) and Preferred Term (PT) by treatment and overall. If a subject had more than one AE for a particular SOC, he/she will be counted only once for that SOC. If a subject had more than one AE for a particular PT, he/she will be counted only once for that PT. In addition, summary tables will include occurrence rates for:

- AE,
- SAE
- Severe AE
- AE related to IM injection
- SAE related to IM injection
- AE related to IV infusion
- SAE related to IV infusion
- IM injection related AE leading to drug withdrawal
- IV infusion related AE leading to drug withdrawal
- AE leading to death
- AE leading to concomitant medication
- AE starting during IV infusion
- AE starting within 24 hrs of end of IV infusion
- AE requiring treatment given.

Adverse events will be coded by the MedDRA coding dictionary, version 19.

4.10 PK Analysis

The pharmacokinetic blood sampling will be listed with the date and time of sampling. This SAP describes only the analyses for the study objectives not involving the PK objectives. The PK objectives will be described in a separate analysis plan.

4.11 Modifications from the statistical section in the protocol

The protocol stated hypotheses with one-sided testing using less than and greater than symbols. This is corrected in the SAP to two-sided hypotheses, as planned, using equal and not equal symbols.

The protocol stated that Cochrane-Mantel-Haenszel test stratified by study site will be used for the primary analysis. However, this conflicts with the primary and key secondary hypotheses planned in the protocol which are not stratified, so this is revised in the SAP to match with the planned hypotheses.

Due to early termination of the study, the sample size will be much less than planned. As a result, the statistical power can be inadequate for the planned

gatekeeping methodology. Therefore, standard hypothesis testing methods may be used instead to analyze the data (see section 4.8).

5. Interim analyses

No interim analyses were planned.

6. Sample size and Power calculations

A total of 330 subjects were to be enrolled and randomized into 3 groups (1:1:1).

The EULAR response rate will be considered as primary parameter. See Appendix B for details on scoring and coding. There is a special interest in the percentage of subjects with an EULAR response category of good or moderate (good and moderate combined) and the percentage of subjects with an EULAR response category of only good. These subjects will be called EULAR responders and EULAR good-responders, respectively.

[redacted]

Primary endpoint:

- The percentage of EULAR responders (good + moderate) at Day 8

Key secondary endpoints:

- The percentage of EULAR good responders at Day 8
- The percentage of EULAR responders at Day 15
- The percentage of EULAR good responders at Day 15

[redacted]

[redacted]

The sample size calculation is based on estimates from [redacted].

Although the above described the planned sample size, the study enrollment did not reach the planned goal, and the study may likely have inadequate statistical power.

7. Tables, Listings and Figures

Below are the titles for the planned study tables, listings and figures

Table 1	Subject Distribution
Table 2.A	Subject Distribution By Center (ITT)
Table 2.B	Subject Distribution By Center (PP)
Table 3.A	Demographics and Baseline Characteristics (ITT)
Table 3.B	Demographics and Baseline Characteristics (PP)
Table 4	Medical and Surgical History (ITT)
Table 5.A	Dose Administration (ITT)
Table 5.B	Dose Administration (PP)
Table 6.A	Dose Administration by Visit (ITT)
Table 6.B	Dose Administration by Visit (PP)
Table 7.A	Dose Administration by Center (ITT)
Table 7.B	Dose Administration by Center (PP)
Table 8.A	EULAR Good/Moderate Responders - Original and Simplified Analyses (ITT)
Table 8.B	EULAR Good/Moderate Responders - Original and Simplified Analyses (PP)
Table 9.A	EULAR Response by Visit (ITT)
Table 9.B	EULAR Response by Visit (PP)
Table 10.A	Time to First EULAR Good/Moderate Response (ITT)
Table 10.B	Time to First EULAR Good/Moderate Response (PP)
Table 11.A	DAS28 Scores (ITT)
Table 11.B	DAS28 Scores (PP)
Table 12.A	Tender and Swollen Joints (ITT)
Table 12.B	Tender and Swollen Joints (PP)
Table 13.1.A	Visual Analog Scale (VAS) – Patient Pain (ITT)
Table 13.1.B	Visual Analog Scale (VAS) – Patient Pain (PP)
Table 13.2.A	Visual Analog Scale (VAS) – Patient RA Disease Activity (ITT)
Table 13.2.B	Visual Analog Scale (VAS) – Patient RA Disease Activity (PP)
Table 13.3.A	Visual Analog Scale (VAS) – Investigator RA Disease Activity (ITT)
Table 13.3.B	Visual Analog Scale (VAS) – Investigator RA Disease Activity (PP)
Table 14.A	American College of Rheumatology (ACR) 20/50/70 Response (ITT)
Table 14.B	American College of Rheumatology (ACR) 20/50/70 Response (PP)
Table 15.1.A	SF-36 Physical Component Score (ITT)
Table 15.1.B	SF-36 Physical Component Score (PP)
Table 15.2.A	SF-36 Mental Component Score (ITT)

8. Statistical software

SAS version 9.3 or higher will be used for all tables, listings and figures.

9. References

LI J., Mehrotra D.V. (2008). Gatekeeping testing via adaptive alpha allocation. Biometrical Journal. 50:708-714

10. APPENDIX A – Scoring and Coding for SF-36 – Short Form 36

Details for scoring SF-36 responses can be found at:
https://www.rand.org/health/surveys_tools/mos/36-item-short-form/scoring.html
Associated SAS code can be found below and at:
http://gim.med.ucla.edu/FacultyPages/Hays/utils/sf36v2-4-public.sas

[redacted]

[redacted]

[redacted]

11. APPENDIX B – Scoring and Coding for EULAR

	Change in DAS28 from baseline		
DAS28 after xx weeks	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2 (inactive)	Good	Moderate	No response
>3.2 and ≤5.1 (moderate)	Moderate	Moderate	No response
>5.1 (very active)	Moderate	No response	No response

12. APPENDIX C – Scoring and Coding for DAS28

The DAS28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP), and general health status. The index is calculated using the following formula:

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

where

TJC28 = tender joint count on 28 joints

SJC28 = swollen joint count on 28 joints

ln = natural log

ESR = erythrocyte sedimentation rate (mm/hr)

VAS = visual analogue scale, i.e., patient's global assessment of disease activity (100 mm VAS)

13. APPENDIX D – Scoring and Coding for ACR 20/50/70

The ACR core set of outcome measures and their definition of improvement includes a ≥20% improvement (ACR20) compared to Baseline in both SJC and TJC as well as in three out of five additional parameters: Physician's Global Assessment of disease activity VAS, patient's Global Assessment of disease activity VAS, patient's assessment of pain VAS, HAQ-DI, and acute phase reactant (either CRP or erythrocyte sedimentation rate [ESR]).

Achievement of an ACR50 requires a ≥50% improvement in the same parameters and an ACR70 requires a ≥70% improvement.

14. APPENDIX E – Scoring and Coding for HAQ

The Stanford HAQ-DI is a patient-oriented outcome assessment questionnaire specific for RA. It consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each question asks on a scale ranging from 0 to 3 if the categories can be performed without any difficulty (scale 0) up to cannot be done at all (scale 3).
The patient must have a score for at least 6 of the 8 categories. If there are less than 6 categories completed, a HAQ-DI cannot be computed, whether the missing categories are due to missing values or they do not apply to the respondent.
In the event where there is a missing domain score but a corresponding aid or device is listed, then the score for that domain will reflect the use of the aid or device, i.e. it will be scored as 2.
If a domain consists of two questions and one response is missing, then the domain score will be the non-missing response but if both responses are missing, the domain score will be missing. If a domain consists of three questions and one response is missing, the domain score will be highest of the non-missing responses, but if two or more responses are missing, then the domain score will be missing.
The HAQ-DI will be set to missing if more than two of the domain scores are missing. In the event that one or two domain scores are missing the final HAQ-DI score will be derived by dividing the total of the remaining domain scores by the number of non-missing domains.

The HAQ-DI is usually analyzed by calculating scores. In each dimension ("dressing & grooming", "arising", "eating", "walking", "hygiene", "reach", "grip", "activities") the raw score is calculated as Max (Dimension Score) and corrected if aids and devices were used or help from another person was needed. When aids or devices or help are indicated by the patient, the score for the category item is raised from a 0 or a 1 to a 2, but if the patient's highest score for that sub-category is a 3, it stays a 3. The available categories scores are summed and divided by the number of categories answered which yields the Standard Disability Index.

15. APPENDIX F – Scoring and Coding for FACIT

The symptom-specific measure FACIT-F (Functional Assessment of Chronic Illness Therapy - Fatigue) was developed to assess chronic illness therapy with special emphasis on fatigue in the past 7 days and consists of 5 dimensions:

1. physical well-being (PWB: 7 items),
2. social/family well-being (SWB: 7 items),
3. emotional well-being (EWB: 6 items),
4. functional well-being (FWB: 7 items), and
5. additional concerns (FS: 13 items).

Each of the questions is categorically answered using the scales 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much. The values of some items are reversed during score calculations, so that higher score values indicate more favorable conditions: negatively stated items are reversed by subtracting the response from '4'. Apart from the single dimension scores, 3 composite scores can be derived based on the 5 dimensions:

FACIT-F trial outcome index (TOI) with a potential range of 0 to 108,

FACT-G total score with a potential range of 0 to 108, and

FACIT-F total score with a potential range of 0 to 160.

The 13 items included in the dimension "additional concerns" will be used to calculate the brief score for FACIT-F (fatigue) scale (potential score range: 0-52).

When there are missing data, pro-rating subscale scores are acceptable as long as more than 50% of the items are answered in that subscale. Subscale scores can be prorated by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered:

Prorated subscale score=[Sum of items scores] x [N of items in subscale]/[N of items answered] .

The total score is then calculated as the sum of the unweighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as overall item response rate is greater than 80% (i.e., at least 22 of 27 FACT-G items completed: first 4 domains).

To derive a FACIT-F Trial Outcome Index (TOI):

_____ + _____ + _____ =_____=FACIT-F TOI
(PWBscore) (FWBscore) (FSscore)

To Derive a FACT-G total score:

_____ + _____ + _____ + _____=_____=FACT-G Total score
(PWBscore) (SWBscore) (EWBscore) (FWBscore)

To Derive a FACIT-F total score:

_____ + _____ + _____ + _____ + _____ =____=FACIT-F Total score
(PWBscore) (SWBscore) (EWBscore) (FWBscore) (FSscore)

The Fatigue Subscale score is calculated as follows: the individual items scores are summed, multiplied by 13 and divided by number of items answered.
