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

Published: 06-10-2015
Last updated: 19-04-2024

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)....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON45232

Source
ToetsingOnline

Brief title
Nanocort vs Depo-Medrol® in subjects with active RA

Condition

- Autoimmune disorders

Synonym
Active Rheumatoid Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Sun Pharma Global FZE
Source(s) of monetary or material Support: Sun Pharma Global FZE

Intervention

Keyword: active Rheumatoid Arthritis, Depo-Medrol, Nanocort

Outcome measures

Primary outcome

Primary Endpoint: European League Against Rheumatism (EULAR) responder

(moderate and good combined) rate at Week 1 (Day 8)

Secondary outcome

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:

* 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

* Assessment by monitoring cortisol levels at Screening, Baseline, 6 and 12 weeks

* 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

Study description

Background summary

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. Prednisolone and some other glucocorticoids 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. Besides a poor safety profile, also poor localization in inflamed areas in the body limits the usefulness of glucocorticoids in the patient. Prednisolone sodium phosphate 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 IM corticosteroids and so has a safety advantage.

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

Study 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 Intravenous Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) will be compared with intramuscular 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.

Intervention

A total of up to 330 subjects will be enrolled and randomized into 3 groups indicated below: *
1) Nanocort 75 mg IV infusion and IM saline injection (110 subjects) *
2) Nanocort 150 mg IV infusion and IM saline injection (110 subjects) *
3) Depo-Medrol® 120 mg IM injection and IV saline infusion (110 subjects)

Study burden and risks

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 will take place; at each visit the subjects have to fill out questionnaires. For details please see Protocol 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 AE*s typically associated with the administration of glucocorticoids have been observed.
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. 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion 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. Willing and able to comply with the study protocol visits, assessments and accessible for follow up.
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*), 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.

Exclusion criteria

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 HIV antibody screen, based on the current medical data of the patient.
6. Abnormal hepatic function (ALT/AST or bilirubin > 2 x upper limit of normal) at the time of the Screening Visit.
7. Abnormal renal function (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 Principal Investigator.
9. Treatment with oral, rectal or injectable (including intra-articular) glucocorticoids (GC) within 6 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
10. Contraindication for glucocorticosteroids
11. Neuropathies or other painful conditions that might interfere with pain evaluation, as judged by the Investigator.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-03-2016
Enrollment:	180
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Depo-Medrol
Generic name:	methylprednisolone acetate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nanocort
Generic name:	Pegylated Liposomal Prednisolone Sodium Phosphate

Ethics review

Approved WMO Date:	06-10-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-11-2015
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-07-2016
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002924-17-NL
ClinicalTrials.gov	NCT02534896
CCMO	NL54447.041.15