Ver 3 contains just the addition of names and contact information for Uddevalla and Göteborg and Örebro

Ver 4 contains only the addition of names and contact information in Örebro and Uppsala

Ver 5 contains a change by removing the exclusion criterion crepitation, as well as changing the study timeline

ver 6 contains only additions of name and contact information in Trollhättan and schedule is updated on page 16

Study Protocol

Pain relief after an intraarticular injection of methylprednisolone vs. placebo in patients with arthralgia in the jaw joint. A randomized controlled blinded multicenter study

Abbreviated title: Methylprednisolone TMJ

Sponsor

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Västerås 2016-06-22

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Göran Isacsson
Associate professor, senior consultant
Coordinating investigator, sponsor

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Pain relief after an intraarticular injection of methylprednisolone vs. placebo in patients with arthralgia in the jaw joint. A randomized controlled blinded multicenter study

SYNOPSIS

Arthralgia (unspecified pain) in the jaw joint is a common condition at a specialist clinic for orofacial pain and jaw function. The treatment aims to alleviate the pain and improve the jaw function. This is done by jaw training, analgesics and / or NSAIDs and unloading the jaw joint with oral appliances. Intra-articular (I.A) injection of corticosteroids is another common treatment method at a specialist clinic. However, in its recommendations from 2011, the *Swedish Agency for Health Technology Assessment and Assessment of Social Services* states that the scientific evidence is insufficient to assess the effect of I.A. corticosteroids in TMJ arthralgia which therefore is classified as "a knowledge gap"[1]. The corticosteroids on the Swedish market are methylprednisolone (Depo-Medrol®), betamethasone (Celestona®-bifas®), triamcinolonehexacetonide (Kenacort®-T), and triamcinoloneacetonide (Lederspan®).

The hypothesis of this study is that an intra-articular injection with methylprednisolone effectively relieves pain in TMJ arthralgia. The objective is therefore to evaluate the effect of I.A. methylprednisolone vs. placebo for a month. The primary effect variable is reduction of the Visual Analog Scale (VAS)- graded pain at maximum mouth opening.

The study is designed as a randomized, blinded and controlled multicenter trial of 64 subjects (18 years or older) referred to four specialist dental clinics, where the subject, according to defined inclusion and exclusion criteria, meets the criteria for the diagnosis of unilateral TMJ arthralgia. The subject visits the clinic on three occasions; a first enrollment visit, a second treatment visit (baseline) and a third final visit for evaluation one month after baseline. A phone call follow-up is made one week after visit 2. During visits 2 and 3, the subject estimates his/her pain at maximal mouth opening as well as the pain at jaw rest on a VAS scale and completes the JFLS (jaw function scale), GCPS (instrument evaluating the consequences of pain) and PHQ-9 (Depression scale). At the evaluating visit the PGIC (Patient Global Impression of Change) scale is also answered. Clinical jaw function parameters are recorded. Subjects are randomized to intra-articular injection with methylprednisolone or sterile saline solution. Three days before and five days after treatment as well as 3 days before the end of the study, the subject registers his/her pain on a diary form three times a day. This aims to capture the dynamics of pain variation in conjunction with the treatment. Study start is estimated to December 2013. "Last Subject Out" is expected December 2015 and a report completed May 2016.

[1] http://www.sbu.se/sv/Publicerat/Sok-kunskapsluckor/Kunskapsluckor/Glukokortikoid-intraartikulart-vid-kakledssmarta/

[3] http://randomization.com/

INTRODUCTION

Arthralgia in the jaw joint is a common condition seen at a specialist clinic for orofacial pain and jaw function. This descriptive clinical diagnosis is characterized by pain from the jaw-face and where the pain exacerbates when chewing tough and firm food. Mouth opening is painful. The treatment aims to alleviate the pain and improve the jaw function. Routinely this is done by jaw training, analgesics and / or NSAIDs and unloading the jaw joint with oral appliances. Intra-articular, I.A., injection of corticosteroids is another common treatment method at a specialist clinic. In clinical practice, I.A. corticosteroids produce good results in arthralgia, osteoarthritis and arthritis. The drug preparations on the Swedish market are methylprednisolone (Depo-Medrol®), betamethasone (Celeston®-bifas®), triamcinolonehexacetonide (Kenacort®-T), and triamcinoloneacetonide (Lederspan®). However, methylprednisolone is the most commonly used product at a specialist clinic in Sweden.

There are many studies published about the effects of I.A. corticosteroids in the treatment of both systemic as well as local non-specific arthralgia / arthritis. Samiee et al. [8] treated subjects diagnosed with disk displacement without reduction with I.A. corticosteroid in combination with manual mobilization, but without controls, and found a significant improvement in mouth opening by an average of 10 mm. Stoll et al. [9] conducted a retrospective study of juvenile idiopathic arthritis in children, JIA, and found that both the mouth opening and magnetic resonance data of arthritic changes improved after I.A. corticosteroid. In a study on JIA children, I.A. corticosteroid computer tomography was used as a guide at injection [1]. Also that study concluded that the mouth opening increased by at least 5 mm and that 77% of the patients became pain free. However, a systematic review of I.A. corticosteroids in the treatment of JIA [10] concluded that there is no scientific evidence in the literature that I.A. corticosteroid improves mouth opening, reducing radiological changes or normalize mandibular growth in children with JIA. Both Kopp & Wenneberg [11] and Björnland et al. [3] received significant symptom improvements following I.A. corticosteroids in the treatment of TMJ discomfort and osteoarthritis. However, the effects of corticosteroid treatment are difficult to interpret when placebo has not been used in any of the studies. Post-injection pain after a corticosteroid injection is a well-known phenomenon but is not judged in relation to the overall effect of treatment. In a double blind study in patients with TMJ arthralgia / osteoarthritis 1 ml saline injected intra-articularly gave a marked reduction of pain up to one week after treatment [5]. The *Swedish Agency for Health Technology Assessment and Assessment of Social Services* also notes that the scientific evidence is insufficient to assess the impact of I.A. corticosteroids in TMJ arthralgia which therefore is classified as "a knowledge gap.

[3] http://randomization.com/

HYPOTES AND SPECIFIC OBJECTIVES

The hypothesis is that one intra-articular injection with methylprednisolone effectively relieves pain in the TMJ arthralgia. The objective is therefore to evaluate a single injection I.A. methylprednisolone (Depo-Medrol®) vs. placebo in subjects with TMJ arthralgia one month after treatment.

Primarily, the degree of pain relief is evaluated at maximum mouth opening. Secondarily, pain relief is measured at jaw rest, jaw function, the consequence of pain, the influence of the mood on pain relief. Also the pain's variability 3 days before, 5 days after the injection and for 3 days before evaluation are described.

ABBREVIATIONS AND DEFINITIONS OF TERMS

CRF	Case Report Form
MIO	Maximal incisal opening
LTR	Laterotrusion
PTR	Protrusion
VAS	Visual Analog Scale
I.A.	Intra-artikular
ITT	Intension-To-Treat
JFLS	Jaw Function Limitation Scale
GCPS	Graded Chronic Pain Severity Scale
PP	Per Protocol
PHQ-9	Subject Health Questionnaire-9
PGIC	Patient Global Impression of Change
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

MATERIALS AND METHODS

The study is designed as a randomized blinded, controlled, multi-center trial with two parallel groups of a total of 64 patients referred to the respective specialist dental clinic.

The study team at each center consists of two dentists and a study nurse. The subjects visit the clinic on 3 predefined occasions and have one scheduled telephone contact.

Visit 1: Enrollment, subject information and informed consent. Assignment of enrollment number. Clinical examination is performed by dentist # 1 or #2. Questionnaires are handed out. In addition, the patient is instructed how to rate the pain on a paper-based VAS scale.

Visit 2: This visit, which may coincide with visit 1, will be done within a maximum of 2 weeks after enrollment visit. Questionnaires are returned to the study nurse. After checking the inclusion and exclusion criteria, the patient is randomized by opening a sealed envelope describing the treatment choice. Dentist # 2 performs the injection treatment with the assistance of the study nurse. The subject

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is not allowed to see which substance is being injected. The subject then receives information how to handle post-injection symptoms. The subject is instructed to rate his/her pain on a paper VAS diary scale for five days immediately after the treatment visit and three days immediately before visit 3. The use of oral analgesics/NSAIDs during these days is also noted in the diary. The papers are returned to the clinic by surface mail.

Telephone contact: One week (± 2 days) after visit 2. The study nurse calls the subject who responds to questions on adverse reactions and is reminded to send in the diary.

Visit 3: One month (± 7 days) after visit 2. Only dentist # 1 registers all information, collect questionnaires and performs a clinical examination. The subject is then finished within the framework of the study. If further treatment is necessary such is given outside the study protocol. Subjects who, for various reasons, undergo some form of treatment for their arthralgia during the study period are not valid for a Per Protocol (PP) analysis but are reported in the Intention-To-Treat (ITT) evaluation.

Table 1. Schedule of trial events from enrollment visit to end of study

	Visit 1 Enrollment	**Visit 2 Treatment Baseline**	**By phone Control**	**Visit 3 Evaluation Study end**
	0 - 2 w before baseline	**Day 0 baseline**	**1 w ± 2d after baseline**	**4w ± 1w after baseline**
Inclusion- exclusion criteria	**x**	**x**		
Informed consent*	**x**			
Randomization**		**x**		
Case history, health declaration	**x**			
Clinical examination	**x**	**x**		**x**
Questionnaires (handed out)	**x**	**x**		
Questionnaires (returned)		**x**		**x**
Injection		**x**		
Adverse events open question		**x**	**x**	**x**
Adverse events observed		**x**		**x**

*** Allocation of enrollment number, ** Allocation of randomization number**

[3] http://randomization.com/

Subjects

Number of subjects

This study is expected to include 64 subjects evaluable in a PP analysis from 4 trial sites in Sweden. The intension is to include a minimum of 10 subjects per center. Subjects who interrupt the study or who are not evaluable are replaced by including other subjects with the lowest possible number.

Subjects referred to resp. specialist clinic are screened for inclusion in the study. Those who meet the criteria for the diagnosis arthralgia according to DC/TMD [6] are the target group for this study. Selection criteria have been chosen to avoid diagnosis such as arthritis/osteoarthritis, disc displacement with/without reduction.

Criteria for diagnosing arthralgia

Criteria that both need to be met:

- The subject responds positive to the question: Have you had pain in jaws, temple, in front of the ear or in the ear during the last month
- The pain changes at jaw movements, function or parafunction

In addition, the subject must report recognized pain in at least one of the following provocation tests

- Palpation of the lateral pole or around the pole
- Maximum assisted / unassisted mouth opening, lateral movement right / left, or protruding movement of the jaw.

Inclusion criteria

- age $\geq$ 18 years
- the diagnose arthralgia in one jaw joint
- understands Swedish verbally and in writing
- In writing give his consent to participate

Exclusion criteria

- jaw sound in the form of clicking (crepitation allowed)
- polyarthritis /connective tissue disease
- bilateral arthralgia
- fibromyalgia or other generalized pain
- ongoing virus or bacterial infection
- ongoing dental treatment
- corticosteroid injection in the jaw past six months
- previous surgery of troublesome joint
- complex psychiatric / psychological profile, institutional residence
- employee at the trial clinic
- hypersensitivity to local anesthetics
- hypersensitivity to methylprednisolone

3 http://randomization.com/

- haemophilia
- methemoglobinemia
- breastfeeding
- serious health conditions according to the examiner's assessment
- take any of the medicins Ciclosporin, Erythromycin, Phenobarbital, Itraconazole, Ketoconazole, Rifampicin, Acetylsalicylic Acid, Oral Anticoagulants
- employee at the trial clinic
- mentally ill and institutional residents including prisoners

Test drugs

Test product: Depo-Medrol 40 mg / ml suspension for injection (methylprednisolone acetate). Pfizer AB, 191 90 Sollentuna

Comparative substance: Sodium chloride Braun 9 mg/ml diluent for parenteral use. B. Braun Melsungen AG, Carl-Braunstrasse 1, D-34212 Melsungen, P.O. Box 1120, D-34209 Melsungen, Germany.

Both preparations are ordered from the hospital pharmacy where the substances are delivered in their original packaging. No special blinding is performed by the preparation for trial (see section Blinding).

Traceability: Each clinic keeps a log of the preparation's batch number and the name of the delivery pharmacy.

The choice of Depo-Medrol as a test substance is motivated by the fact that it is the corticosteroid most commonly used for intraarticular injection at Swedish TMD specialist clinics.

Treatment - intervention

Both clinical examination and treatment in this study are conducted according to the routines provided by participating clinics in the care of this group of patients. The dose of methylprednisolone is also the one routinely given in TMJs and follows the SmPc instructions.

Injection Procedure

The treatment is initiated with a nerve block of n. auriculotemporalis with 1.8 ml Citanest-Octapressin®. This anesthesia is injected outside the articular capsule in order avoid interfere with the intra-articular injection. The skin is thoroughly washed with 70% ethanol and dried off. All handling of the injectable occurs under aseptic conditions and with sterile gloves. Operator together with study nurse prepares the syringe behind the subject who is positioned leaned back in the treatment chair without seeing the injectable. With the jaw in a relaxed position, the lateral condyle pole is identified. The subject is asked to open his/her mouth and the injection needle (gauge 0.7 mm) is moved forward

[3] http://randomization.com/

until contact is obtained with the cartilage of articular tuberculum to identify the upper joint compartment. Aspiration attempts are made and, if present, exudate is aspirated. One ml of methylprednisolone or 1 ml of saline is injected slowly in this position. The procedure is finalized by covering the skin with a bandage.

Before the start of the study, all investigators are instructed in the injection technique are calibrated for the clinical examination.

Situations when dosing of the drug must be discontinued: In cases where the subject, in conjunction with the injection of test substance, signals that it does not wish to complete the injection, the procedure is interrupted. Also, in cases where the subject exhibits an abnormal bodily or psychological / psychological response, the procedure is interrupted. If the protocol-defined dose or part thereof has been injected, the subject is included in the ITT assay. Those subjects who do not want to complete the injection or if the examiner interpret the subject not being able to complete the procedure are offered other treatment outside the protocol. The reason for early interruption of the study is recorded in the "Study end" CRF module. If the cause of early interruption is considered to be an incident / deviating reaction, is also recorded in the CRF module "Health incidents".

Other treatment

Other medication necessary for the patient's care may be given after the examiner's judgment. All subjects may take analgesics as rescue in the form of paracetamol or ibuprofen if necessary. The amount and type of analgesics are recorded daily 5 days after treatment and three days prior to the evaluation visit. However, the subjects are not allowed to take analgesics / NSAIDs three days prior to the treatment. Administration of all drugs during the study is recorded.

Those who use oral appliances before enrollment continue with their appliances at the same routine throughout the study time. Any new treatment is not allowed during the study period. If, for various reasons, the subject nevertheless commences any form of treatment other than the study drugs, then subject is not valid for a PP analysis but is included in the ITT analysis.

Care after the trial

If the subject still has complaints from the jaw at the evaluation visit, additional treatment is offered according to the clinic's routine.

Measurement methods and variables

The effect variables refer to the difference between the baseline and the evaluation visit.

Primary effect variable: The change in VAS-assessed pain at maximum mouth opening

Secondary variables: The change of VAS-assessed pain at the jaw test.

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A 100 mm visual analog scale, VAS, with the end definitions "no pain" and "unbearable pain" will be used to measure the intensity of pain both at maximum mouth opening and at jaw rest.

VAS_{point} estimation is recorded on paper at baseline immediately prior to injection and at the evaluation visit. A diary was also used to register $VAS_{diary\ pain}$ in the morning, noon, and evening for three days immediately prior to the treatment day as well as five days after treatment and 3 days prior to the evaluation visit.

For those subjects where visits 1 and 2 coincide, there is no opportunity to register the pain on forms three days before treatment, but these subjects are considered valid for a PP analysis if other protocol criteria are met.

JFLS: A 0-10-graded jaw function scale with 20 questions where the subject grades its jaw function last month. [7]

GCPS: An 8-point instrument where the subject answers how the pain on a 0-10 gradual scale of 6 of the questions has affected the life and its consequences. Two of the questions address the duration of the pain [4].

PHQ-9: An instrument with a 4-graded scale with 9 questions describing the mood.

Secondary effect variable used only at the evaluation visit

PGIC: The respondent answers the question "How has your pain changed compared with the time before the injection?" Enter the alternative that best describes the situation on average. Seven response options " very much better, much better, a little better, unchanged, a little worse, much worse, very much worse "[2].

Secondary effect variables - clinical registration

Maximum mouth opening (distance between the incisal edges + vertical overlap measured at one of the central incisors)

- Maximum mouth opening without pain (mm)
- Maximum mouth opening with pain (mm)
- Maximum mouth opening with assistance (mm)

Palpation tenderness TMJ

- Over the lateral condyle pole (yes / no)
- Pericondylar (yes / no)

All recordings of the jaw system will be made according to the DC-TMD criteria and its protocols [6].

REGISTRATION OF SAFETY

Incident (adverse event) definition: An incident is an accidental and unfavorable sign or symptom of disease associated with the use of a drug, whether it has a causal link with the product. The severity is judged to be "serious" (SAE) or "non-serious"

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A SAE is defined as

- Results in deaths
- Is life-threatening
- Requires hospitalization or extends ongoing hospitalization
- Resulting in permanent or significant disability
- Congenital anomaly / birth defect

The investigator shall judge the causal link between the study intervention and the serious incidence according to the following classification:

1. Probably related. There is a time causal link. No other causal factors exist.
2. Possible related. There is a time causal link. Other causal factors may exist.
3. Not Related. No temporal causation or doubtful and / or other safe or probable factors exist

Incident registration procedures: Information about incidents is recorded from the date of drug administration until the end of the study one month after treatment.

At the end of the treatment visit, during the evaluation visit and subsequent follow-up phone calls, the subject will be asked if they experienced any incident through the following standard questions:

"Have you had any health problems since you received treatment?"
"Have you had any health problems with your jaw since you received treatment?"
"Have you had any health problems since leaving the clinic?"
"Have you had any health problems with your jaw since leaving the clinic?"

In addition, events spontaneously reported by the subject or observed by the study staff from the time when the study drug is administered, is registered and followed until study end. All incidents are recorded on CRF.

The intensity of incident is graded as mild, moderate and severe:

Mild: Awareness of clinical findings or symptoms but which is easily tolerated
Moderate: Discomfort to such an extent that it affects normal activities
Severe: Performance impairment to the extent that normal activities cannot be performed

Symptoms of the disease during the study: Local reactions will be reported as an incident if there is a significant change compared to baseline. Pain and jaw function impairment from the time of injection of the drug the to study end will be recorded as an effect parameter and not as an incident.

Report of incidents: Coordinating investigator / sponsor is responsible for informing the Medical Products Agency and the Ethics committee of any serious incidents and serious unexpected reactions, such as Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting as well as annual safety reporting.

Reporting of serious incidents: The investigator and the staff at each test site are advised to report to the sponsor within one day (immediately and no later than the end of the next weekday) all SAEs that arise during the trial period. The sponsor, together with the investigator, collects all necessary

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information to report to the Medical Products Agency and the Ethics Committee in Uppsala within seven days after the sponsor received information of an incident. Additional relevant information on the consequences of the incident should be reported to the Medical Products Agency and the Ethics committee within further eight days.

The sponsor shall register and report as soon as possible all other suspected serious unforeseen side effects to the Swedish Medicines Agency and the Ethics committee in Uppsala. The reporting must be done within 15 days from the date the sponsor first became aware of them.

If a non-serious incident changes to becoming an SAE, then the SAE reporting routine should be followed.

All SAEs should be reported regardless of whether or not it is considered to be a causal link with the study drug. All SAEs must be documented in the "Health Incidents" section of CRF.

The sponsor shall inform all investigators of suspected serious unforeseen incidents. This is done continuously as soon as a SAE has been reported to the authorities.

In case of pregnancy: Pregnancy in itself is not considered to be an adverse event if there is no suspicion that the test substance may have interfered with the effect of contraception. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject interrupts the study. All reports of congenital abnormality are SAEs. Spontaneous miscarriage should also be treated as SAEs. Elective abortions without complication should not be treated as AEs. All pregnancies must be reported to the sponsor during the trial period as well as when the outcome of pregnancy is known. Complications during pregnancy should be registered as AE and considered as SAE if they fulfill any of the criteria for an SAE.

Security Monitoring: No special safety committee is planned. The sponsor will continually assess security data after reporting from responsible investigators at the respective center and monitor. In cases of serious incidents or adverse events, specialist physicians are consulted at the Center for Clinical Research, CKF, Västmanland Hospital Västerås, prior to reporting to the Pharmaceutical and Ethics Committee in Uppsala.

When the first 20 subjects have undergone the evaluation visits, CRF is signed and monitor "picked home" data, a comprehensive safety assessment is made. If the compilation of health incidents deviates significantly from Depomedrol SmPC, a temporary interruption of the study is made until its causes and effects are assessed by the specialist physicians at CKF and possibly in consultation with the Medical Products Agency / Ethics Committee. If this analysis indicates incidents / side effects such as mild (but not described in SmPC), an update of the information communicated to the subjects is provided for informed consent, the ethics committee is informed / giving approval and the study

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resumed. If the analyses indicate systemic serious incidents / adverse reactions that are judged to increase the risk for the subjects, the study is definitely discontinued.

RANDOMIZATION

Randomization list is generated by computer[3] and each randomization should be balanced with as many subjects in the treatment group as in the control group. The randomization, which is sealed in individual envelopes, is performed by a person who is not attached to the project and also keeps the randomization list locked up. The envelopes contain the randomization number and description of the substance to be injected. The envelope is opened immediately before the treatment and after all inclusion criteria and exclusion criteria are met.

BLINDING

Placebo solution similar to the whitish opaque cortisone solution cannot be produced. Masked syringe can not be used when aspiration is always done before injection and this requires transparent syringe. Dentist # 2 and the study nurse will therefore know which substance is being injected. The subject is not allowed to see the vial or syringe and is therefore blinded. Dentist # 1 collecting forms and completes the clinical examination (visit 3) is also blinded to the choice of injection solution.

STATISTICAL METHODS

Tolerability and safety evaluation are based on all subjects in which trial drugs have started to be injected. The primary effect analysis, Intention-To-Treat, is based on all subjects who have undergone a baseline examination and received a study drug. A distinctive per protocol analysis is also made on the group of subjects who follow the study of the protocol without major deviations.

Calculation of sample size (power)

The primary variable, VAS pain at maximum mouth opening, is a continuous response variable with an independent control and with an equal number of actively treated as controls. Published data from studies with I.A. corticosteroid are noted that each person was normalized by a standard deviation of 20. If the true difference between experimental and control is on average 15 a number of 32 experimental subjects and 32 control persons are needed to reject the null hypothesis that the population average in the experimental group is equal to the control group with a likelihood of 0.8. The probability of type 1 error with this test of the zero hypothesis is 0.05.

The treatment group will be compared with the placebo group using the Wilcoxon test and an associated 95% confidence interval of the subject's absolute change from baseline. The protocol describes the absolute change of VAS score at maximum mouth opening baseline to study end (1 month) as the primary effect variable. The diary's recordings of pain are calculated as an average for each subject and are graphically described for the days when such registration is made. No correction

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for multiplicity will be used. Descriptive analysis of all variables will be performed.

Randomized, but untreated subjects are not considered to be valid for analysis. Subjects randomized and treated but who are not coming to the evaluation visit are evaluated in an Intention-To-Treat analysis.

PATIENT RECORDS, MONITORING AND DATA HANDLING

An independent monitor from the Center for Clinical Research (CKF) Västmanlands Läns Landsting will check the source data of the study against the data specified for the study's variables as well as for safety records, all specified in a special monotoning plan (not attached). CRF from the different centers will be collected by the monitor and staff at CKF will enter the data into the research database and establish "clean file" when all study data is entered and checked.

The patient's record must state the name of the trial, the randomization number, the date when the candidate signed informed consent, indication that all inclusion / exclusion criteria have been met, as well as the date when the examiner terminates or interrupts the study. The record should also indicate how the code can be broken in emergency cases, as well as information on diagnosis and administration of trial drugs.

The examiner and the sponsor establish and keep the documents containing data recorded in the course of the study. The data is made available in readable condition at the request of the Medical Products Agency throughout a filing period of 10 years after completion of the trial. The archiving of all the data from the study takes place at Västerås CKF, and data files are protected by privacy rules, the Archives and the Subject Data Acts. The respective clinic also archives the data from its subjects under the same regulatory system.

REPORTING AFTER THE END OF THE TRIAL

Within ninety days after the trial has been completed at all trial clinics, the sponsor shall report to the Medical Products Agency and the Ethics committee in Uppsala that the trial has been completed. If the trial is terminated prematurely, the sponsor shall immediately and no later than fifteen days inform the Medical Products Agency and the Ethics committee in Uppsala. The sponsor shall state the reasons for termination of the trial and, where appropriate, the follow-up measures taken for safety reasons.

TIMETABLE

Ethics review to be submitted August 2013

Pharmaceutical examination to be submitted August 2013

Information and logistics planning September-October 2013

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Study start December 2013, completion end December 2016

Data processing, analysis and reporting February - May 2017

Summary report submitted to the Swedish Medicines Agency by July 2017

ETHICS

Ethics evaluation will be submitted to the Ethics Committee Uppsala. This study will be conducted in accordance with the Helsinki declaration principles.

The final study protocol, including trial information and the informed consent, must be approved by the Ethics Committee before any subject is enrolled in the study.

The investigator is responsible for ensuring that each subject receives complete and adequate oral and written information about the study and its performance, purpose, risks and benefits. Time should also be given so the subject can ask questions and, if possible, give time for consideration. The examiner is responsible for ensuring that all subjects give written consent before enrollment is made.

The subject should also be informed that at any time, he/she may interrupt its participation in the study without affecting their treatment at the clinic.

Insurance: The subjects are covered by the respective centers patient's insurance and by the Medical drug insurance.

CONSEQUENCES AND RISK EVALUATION

Risk-benefit evaluation

The purpose of this study is to help fill one of knowledge gaps and be a valuable addition to increasing the quality of treatments made on the group of people diagnosed with arthralgia in the jaw joint. The benefit-risk balance in the trial is therefore considered positive when considering the items below.

Potential risks and considerations are

1. Administration of intra-articular methylprednisolone as well as the risk of complications resulting from the procedure
2. Interactions with other drugs intended for diseases other than those in this study as well as the risk of local anesthetics which is a part of the study procedure.
3. Hypersensitivity to drugs used in the study
4. Particularly vulnerable groups
5. Incomplete / poor effect of study drug
6. Ethical considerations

1. Injection of intra-articular corticosteroids is a routine. Despite proven good effects on arthritis, there are also well-known side effects. Post-injection pain the days after treatment is common and in repeated injections there is a risk of skin atrophy at the injection site. The reason for intra-articular

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deposition instead of other parenteral or oral administration is that a higher concentration of drug at the target organ is obtained. The risk of infection resulting from the injection is considered negligible following proper skin wash with 70% ethanol and using sterile gloves. The protocol describes this in the section "Injection Procedure". It should be noted that 70% ethanol is used without the addition of chlorhexidine which is ototoxic.

As pain is detected during the various stages of the trial, the study will provide a picture of pain as a part of the disease as well as the result of the treatment. In this way, the risk benefit of the treatment can be assessed from an efficacy perspective.

Hemophilia is an exclusion criterion as injection into joints may cause intra-articular hemorrhage

2. The drugs that, according to SmPC, have interactions with methylpredisolone (Ciclosporin, Erythromycin, Phenobarbital, Itraconazole, Ketoconazole, Rifampicin, Acetylsalicylic Acid, Oral Anticoagulants) are an exclusion criterion.

Citanest Octapressin® used for nerve blockade is considered to have no interaction with methylpredisolone. Citanest (prilocaine) is considered to be the least toxic of local anesthetics marketed in Sweden. Octapressin may exacerbate methemoglobinemia and persons with such diagnosis are excluded.

3. Hypersensitivity to drugs used in the study is set as exclusion criteria

4. Particularly vulnerable groups are children, mentally ill-fated, institutional residents including prisoners, employees and persons with serious health conditions. All these groups are covered in the exclusion criteria.

5. In case of incomplete / poor effect of study drug "rescue medication" is allowed

6. Use of placebo solution is an ethical consideration. Corticosteroids must be regarded as a "gold standard" in local drug treatment of painful joints, but studies have shown that intra-articular saline results in significant symptomatic relief. The latter may be explained by the dilution of pain-triggering mediators in the joint. The subject is allowed to take rescue medication and further treatment is provided outside the study protocol to all those who have not received adequate relief from the study drug. This applies to both those who interrupt the study in advance and those who complete the month-long study. The benefit of the study is therefore considered to be greater than the risk.

[3] http://randomization.com/

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