

Ruprecht-Karls Universität Heidelberg

Institut für Medizinische Biometrie und Informatik

Koordinierungszentrum für Klinische Studien (KKS Heidelberg)

# **Meta-analysis of S-Adenosylmethionine and Oxaceprol in treatment of Osteoarthritis**

## **Protocol**

**Final version**

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# Protocol: Meta-analysis of S-Adenosylmethionine and Oxaceprol in treatment of Osteoarthritis

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## 1. Study outline

Title:	Meta-analysis of S-Adenosylmethionine and Oxaceprol in treatment of osteoarthritis.
Sponsor:	Arzneimittelkommission der deutschen Ärzteschaft
Indication:	Osteoarthritis
Primary objective:	To combine the evidence of the single trials concerning the efficacy of S-Adenosylmethionine and Oxaceprol in the treatment of osteoarthritis.
Secondary objective:	To evaluate the quality of the trials regarding (new) guidelines.
Design:	Meta-analysis based on published or unpublished data of randomized clinical trials comparing S-Adenosylmethionine or Oxaceprol and placebo or standard therapy in the treatment of osteoarthritis.
Study selection criteria:	Open, single-blind and double-blind randomized controlled clinical trials comparing Oxaceprol or S-Adenosylmethionine with placebo or standard therapy in patients with osteoarthritis. Any dosage form and schedule of Oxaceprol or S-Adenosylmethionine is eligible. At least one of the endpoints (primary or secondary) must be given in the publication. No time frame or publication language will limit the number of trials in this meta-analysis.
Primary efficacy endpoint	“best” available pain-score
Secondary efficacy endpoint	“best” available function-index
Literature search strategy	medline, embase, club, references

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## **2. Introduction**

This meta-analysis should support the review of the efficacy of Oxaceprol and S-Adenosylmethionine in osteoarthritis.

### **2.1. General Information**

Client	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Köln
Principle Investigator	Prof. Dr. N. VICTOR
Responsible Biometrician and Project-Manager	Dipl.-Math. S. WITTE
Reading Group	Dr. U. MANSMANN Prof. Dr. N. VICTOR Dipl.-Math. S. WITTE
Medical Expert Group	Prof. Dr. R. LASEK, Köln Prof. Dr. Dr. h.c. K. BRUNE, Erlangen (clinical / pharmacological) Prof. Dr. K. L. SCHMIDT, Bad Nauheim (clinical / rheumatological)

### **2.2. Medical background**

Osteoarthritis is one of the dominant diseases of the elderly patient. About 50% of those older than 60 years of age suffer temporarily or permanently from pain resulting from osteoarthritis. Two types of remedies are recommended: One type is geared towards improving acute pain and swelling, i.e. the inflammatory symptoms. Many analgesic compounds are proven remedies in this respect. Many other substances are claimed to be of effectiveness without sound and sufficient evidence. This situation is much more complicated with respect of disease modification, i.e. re-normalisation of joint structure and function under treatment. Many substances are claimed to have effects as disease modifiers in osteoarthritis (so-called chondro-

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protective agents). The evidence is scarce and not accepted by most researchers as sufficient for proof. A cautious independent and state of the art evaluation of such studies is mandatory and timely. The overall evidence is not known.

## **3. Objectives**

### **3.1. Objectives of the single trials**

To evaluate the therapeutic efficacy of Oxaceprol and S-Adenosylmethionine in patients with osteoarthritis.

### **3.2. Primary objective of the meta-analysis**

To combine the evidence of the single trials concerning the efficacy Oxaceprol and S-Adenosylmethionine in the treatment of osteoarthritis in order to support the review of both drugs in that indication.

The aim of meta-analyses is to estimate the treatment effect more precisely than any single trial (provided study results are homogeneous). Owing to the higher number of patients, better precision and a reduction in the bias of the estimate are expected.

### **3.3. Secondary objective of the meta-analyses**

To evaluate the quality of the trials regarding the guidelines “Design and conduct of clinical trials in patients with osteoarthritis”<sup>1</sup> based on the information given in the publications.

## **4. Study design**

This is a meta-analysis based on literature data of randomized clinical trials for the comparison of Oxaceprol or S-Adenosylmethionine and placebo or standard treatment regarding osteoarthritis.

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## **5. Time schedule**

A biometrical report will be provided after 3 months from the signature date of the contract on. Delays (not caused by to the KKS) might delay the report.

## **6. Identification of trials**

A list of some trials investigating Oxaceprol or S-Adenosylmethionine were provided by the AkdÄ.

Electronic search of studies via MEDLINE and EMBASE ([www.dimdi.de](http://www.dimdi.de)) using the following strategy in the time frame of January 1966 to June 2000.

(CT DOWN ?arthr?) AND (CT DOWN ?adenosyl? OR TE DOWN ?adenosyl? OR CT DOWN ademet? OR TE DOWN ademet?) AND (PPS=human OR CT=human) AND (DT=Randomized Controlled Trial OR DT=meta?analysis OR CT=Randomized Controlled Trial OR CT=meta?analysis)

or

(CT DOWN ?arthr?) AND (CT DOWN oxace? OR TE DOWN oxace?) AND (PPS = human OR CT = human) AND (DT = Randomized Controlled Trial OR DT = meta?analysis OR CT = Randomized Controlled Trial OR CT = meta?analysis)

Electronic search of studies via Cochran-Collaboration ([www.clib.de](http://www.clib.de), [www.update-software.com](http://www.update-software.com)) searching for osteoarthritis (abstracts and reviews) and checking all findings by hand. Additionally all titles in the reference list of the literature finding will be scanned for further trials.

## **7. Data collection / extraction**

An extraction sheet will be designed to extract the data from the publications.

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## 8. Selection of trials

Two independent scientists (reading group) review the literature / trials to select the bunch of studies for analysis after identification of the trials.

### 8.1. Criteria for inclusion / exclusion of trials

A trial will be included in this meta-analysis if each of the following conditions are fulfilled. The list gives an order for the inclusion which will be used for the presentation of the reasons for exclusion of trials.

<b>1. Indication:</b>	Trials in the treatment of osteoarthritis (gonarthrosis, coxarthrosis, spondylarthrosis, ...).
<b>2. Medication:</b>	Any dosage form and schedule of Oxaceprol or S-Adenosylmethionine is eligible.
<b>3. Study Design</b>	Controlled, randomised, comparing Oxaceprol or S-Adenosylmethionine versus placebo or standard therapy (open, single-blind or double-blind)
<b>4. Available information:</b>	The relevant results (primary or secondary endpoint of the meta-analysis) of the study are published or an unpublished report providing the main results of the trial is available.

No time frame or publication language will limit the number of trials in this meta-analysis.

### 8.2. Provisional list of trials to be included

At the time of writing, the authors are aware of the following trials which may be eligible for this meta-analysis (handed over by Prof. Dr. R. LASEK):

S-Adenosylmethionine: <sup>5-7,10,12,14-17,23,25</sup> and Oxaceprol: <sup>2,4,18,19,22</sup>.



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## **9. Endpoints in the meta-analysis**

The endpoints described here are those envisaged at the time of planning this meta-analysis. Any modifications of the endpoints that may be necessary will be specified in an amendment. The amendment will be prepared after data collection is finished and a list of the main variables in the single trials is assembled, but *before* the statistical analysis is started. If decisions on cutpoints not specified here are required, they will be made by an independent expert and included in the amendment.

### **9.1. Primary endpoint**

The primary efficacy variable is a pain-score. If there are more than one pain-scores given, one single score should be chosen according to a ordered list of endpoints. A list of endpoints in the original trials will be rated from the medical expert group. For this rating the following issues should be considered.

- clinical relevance of the pain-score
- pain-score is usual and / or validated
- an aggregated pain-scores is given
- pain-score is also important in the original study (e.g. as the primary endpoint)
- availability of the data

### **9.2. Secondary endpoints**

Furthermore, if possible, a function index will be analyzed.

### **9.3. Additional endpoints**

- The quality of the trials (as far as possible with the publication) will be described descriptively using the guidelines “design and conduct of clinical trials in patients with osteoarthritis – recommendations from a task force of the osteoarthritis research society”<sup>1</sup>.

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- If available the “time to onset” (time to an evident change in an other endpoint, e.g. pain).

## **10. Documentation**

### **10.1. Data Management / Extraction**

The decision whether a study will be included or not will be made independently by two members of the reading group after reading the publication. Where there are contradictory findings, the medical expert group will decide. All excluded trials and the reason for exclusion will be documented.

The relevant information will be extracted from the study publication. Where more than one publication of a study is located, information will be extracted from all articles and pooled. If conflicting results are presented in the different publications of one study, the first author will be asked for clarification. Data extraction will be performed independently by two members of the reading group using a prespecified extraction sheet. Conflicting issues will be resolved by the medical expert group.

A global database including all necessary data will be established. Double entry will be performed.

### **10.2. Data Checking Procedures**

No data checking procedures will be performed.

## **11. Statistical Analysis**

Since meta-analyses are observational<sup>24</sup>, their results, particularly the *P*-value obtained in meta-analyses, do not have the same confidence as the results of controlled clinical trials.

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The two different treatments will be analyzed separately. No comparison will be performed. Each treatment will be compared to placebo and active drug separately. Additionally the different active treatments will define subgroups for subgroup analyses.

A Funnel-Plot, Confidence / Forest-Plot and a Radial / Galbraith-Plot will be presented if possible.

Statistical tests will be conducted two-sided at the 5% level. Only tests of heterogeneity across trials will be carried out at the 20% level. All confidence intervals will be presented two-sided with a coverage probability of 95%. A fixed effects model will be assumed if there is no evidence for heterogeneity. Otherwise a random effects model will be used.

The main hypothesis for the placebo controlled trials is: “treatment group have the same effect regarding the primary (secondary) endpoint”.

The statistical analyses will be performed on a HP-UX 7000/900 workstation using SAS<sup>®</sup> software.

## **11.1. Methodological background**

Two distinct models are generally used to combine independent randomized trials comparing two treatments: the fixed effects model (FEM) and the random effects model (REM). The FEM is based on the assumption that in all studies the same treatment effect is estimated, i.e. homogeneous treatment effects are assumed. In the REM, on the contrary, the treatment effects are assumed to differ from study to study. The trials are considered as a random sample from the population of possible trials<sup>11</sup>.

Suppose that  $k$  trials are included in the meta-analysis and from each trial, an estimator of treatment effect  $\hat{\theta}_i$  ( $i = 1, \dots, k$ ) and its estimated variance  $w_i^{-1}$  are available. In a FEM, the individual estimators of the treatment effect are assumed to be normally distributed around the common treatment effect  $\theta$ :  $\hat{\theta}_i \sim N(\theta, w_i^{-1})$ . The common treatment effect  $\theta$  is estimated by a weighted mean of the single estimators:  $\hat{\theta} = \sum w_i \hat{\theta}_i / \sum w_i$ . The two-sided 95% confidence

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interval is obtained using a normal approximation:  $\hat{\theta} \pm 1.96\sqrt{1/\sum w_i}$ . Based on the global estimator, the null-hypothesis  $H_0 : \theta = 0$  is tested using the test-statistic  $T = \sum w_i \hat{\theta}_i / \sqrt{\sum w_i}$ , which is standard normally distributed under  $H_0$ . This methodology is applicable for any measure of treatment effect. Details are, for example, presented in FLEISS (1993)<sup>11</sup> and BERLIN et al. (1989)<sup>3</sup> and also for ordinal data in WHITEHEAD et al. (1991)<sup>26</sup>.

If the assumption of the FEM is violated, the generalizability of the results to future patients is questionable. A formal test is usually applied to investigate heterogeneity. The null-hypothesis of homogeneous treatment effects is rejected if the test-statistic  $Q = \sum w_i (\hat{\theta}_i - \hat{\theta})^2$  is larger than the critical value of the chi-square distribution with  $k - 1$  degrees of freedom.

If the assumption of a common treatment effect over all studies is not fulfilled, a REM might be more appropriate. The true treatment effects are assumed to be normally distributed with a common expected value  $\theta$  and variance  $\tau^2$ . The global parameter  $\theta$  is estimated in the same way as in the FEM:  $\hat{\theta}^* = \sum w_i^* \hat{\theta}_i / \sum w_i^*$ . Only weights are different:  $w_i^* = (w_i^{-1} + \hat{\tau}^2)^{-1}$ , where  $\hat{\tau}^2 = \max\{0, (Q - (k - 1)) / (\sum w_i - \sum w_i^2 / \sum w_i)\}$  is an estimate<sup>9</sup> of the common variance  $\tau^2$ . To test the null-hypothesis  $H_0 : \theta = 0$ , the test described for the FEM is applied, only weights are replaced by the new weights.

The choice between the FEM and the REM is discussed controversially in the literature<sup>13</sup> and is still unresolved yet<sup>8</sup>. But it is widely accepted<sup>20,21</sup> that in the presence of heterogeneity, a careful investigation of potential sources of heterogeneity is of greater importance than a global analysis, as e.g. a random effects analysis. Moreover, the model assumptions, particularly the normal distribution of the treatment effects and their common variance, have been termed unrealistic<sup>20</sup>. The investigation of heterogeneity is generally very limited in meta-analyses based on published data.

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## **11.2. Potential reasons for heterogeneity**

The following prespecified potential factors for heterogeneity should be investigated if possible (subgroup analyses).

- type of pain-score
- type of active drug
- treatment duration during trial
- year of carrying out the trial

## **11.3. Main analyses**

In case no heterogeneity is found, the individual estimators will be combined into a global estimator using a fixed effects approach (see 11.1). The corresponding confidence interval will be calculated and the global test of treatment effect will be performed. In addition, the estimator of treatment effect with a confidence interval will be presented for each *single* trial. For the primary and secondary endpoints, these results will be summarized in a confidence interval plot.

In case heterogeneity is detected by the test of homogeneity, one major task is the detection of possible reasons for heterogeneity. The potential factors given in (11.2) will be considered. If the heterogeneity can be explained, a random effects model will be used. Otherwise the calculation of a overall efficacy estimate is not possible. Additionally trials making a major contribution to the heterogeneity statistic will be identified. Heterogeneity is expected.

## **11.4. Sensitivity analyses**

In case of a fixed effects model the random effects model will be analysed as a sensitivity analysis. The analysis has explorative rather than confirmatory nature

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## **12. Administrative Aspects**

### **12.1. Initiation of the meta-analysis**

The protocol must be approved by the principal investigator and the responsible biometrician. A copy will be send to the members of the medical expert group before the approvement.

### **12.2. Organizational structure**

The meta-analysis is guided by the principal investigator and conducted by the project manager. The project manager is responsible for the performance of the meta-analysis according to this protocol.

The project has a reading group and a medical expert group.

All essential decisions will be made by the reading group. In particular, it will be responsible for the fact that the meta-analysis is performed in accordance with legal and regulatory requirements. It has to approve the protocol and possible amendments to the protocol. The reading group is also responsible for deciding on the inclusion or exclusion of trials. The members of the reading group will extract the data independently from the publications. Where there are contradictory findings or decisions, the medical expert group will decide.

The communication will be done by circular letters and e-mails. The list of committee members is given in the appendix.

### **12.3. Sponsor's and investigator's obligation**

The meta-analysis will be performed in accordance with the paragraphs concerning meta-analyses of the ICH-E9 guidelines.

### **12.4. Announcement to the authorities**

Announcements are not necessary.

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## **12.5. Protocol amendments**

No changes should be made to the protocol without a written amendment. The reasons for these changes must be given in the amendment which has to be approved by reading group after which it becomes part of the study protocol.

## **13. Patient's privacy**

No patient data will be collected, i.e. the patients privacy won't be touched.

## **14. Report**

The project manager will be responsible for preparing a final biometrical report. The final report will be approved by the reading group.

## **15. Publication**

Publication of the results in a scientific journal is intended. The responsible biometrician will be asked for participating in any publications resulting from this meta-analysis

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## **17. List of Committee members**

### **Principal Investigator and member of the reading group:**

Name: Prof. Dr. N. VICTOR  
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### **Project Manager, responsible Biometrician and member of the reading group:**

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### **Member of the reading group:**

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## **Medical Expert Group:**

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### **18. Approval of the Protocol**

Dates and signatures of the members of the reading committee are necessary to approve this protocol.

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Dr. Ulrich Mansmann

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Prof. Dr. Norbert Victor

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Dipl.-Math. Steffen Witte