

NMSG 8 / 00 July 2001

Efficacy of iv bisphosphonate in health-related quality of life and skeletal morbidity in newly diagnosed multiple myeloma requiring treatment.

A prospective randomized double-blind 'dose-effective' study with 'cost-utility' analysis.

A multicenter study in the Nordic Multiple Myeloma Study Group (NMSG).

CONTENT

0. Summary	Page 3
1. Background	Page 4

2. Objectives	Page 8
3. Statistical assumptions	Page 9
4. Design	Page 10
5. Patient Selection	Page 11
6. and randomization	Page 12
7. Patient Information	Page 12
8. Bisphosphonate treatment	Page 13
9. Investigation and Reporting	Page 15
10. Insurance	Page 15
11. Ethics	Page 15
12. analysis	Page 15
13. Administration	Page 16
14. Projects	Page 16
15. Economy	Page 16
16. Publication	Page 17
17. References	Page 17
NMSG's Working Group	Page 19
Regional Coordinators	Page 20
Annex I - Diagnostic and reponse criteria	Page 21
Annex II - Patient Information - Participation	Page 23
Annex III - Patient Information - Registration	Page 25
Annex IV - Monitoring and Safety Committee	Page 26
Annex V - Summary of studies	Page 27
Annex VI - Practical guidance for the notification of a new patient and start treatment	Page 28

SUMMARY

Multiple myeloma is a malignant blood disease in which the monoclonal plasma cells dominate the marrow. Multiple myeloma cells stimulate osteoclasts to increased activity leading to the decalcification and weakening of the skeleton at increased risk of fractures and bone pain. Symptoms from the skeleton are dominant in multiple myeloma patients and are the main reasons for morbidity and costs of health care.

Bisphosphonates inhibit osteoclast function and have documented efficacy in hypercalcemia of malignancies including multiple myeloma. Three major randomized trials of prophylactic bisphosphonate treatment seem to show symptomatic efficacy in multiple myeloma patients, but the optimal dosage, the effect on patients' quality of life and the pharmacoeconomical consequences of the treatment are unclear. This should be evaluated in a randomized, double-blind study of two pamidronate doses in newly diagnosed multiple myeloma.

Inclusion criteria: All newly diagnosed multiple myeloma patients requiring treatment in NMSG's record area in Denmark, Norway and Sweden.

Exclusion Criteria: Patients with life expectancy less than 3 months, patients who have been treated with bisphosphonates for more than three months over the last six months, patients who at 4 weeks after start of chemotherapy still have S-creatinine > 400 $\mu\text{mol/l}$, patients who are not expected to conduct monthly intravenous therapy or who do not wish to participate. However, all patients should be registered.

Primary outcome (endpoint): Physical function assessed by the quality of life questionnaire (EORTC QLQ-C30)

Secondary endpoints: Skeletal-related events, cost-utility analysis of quality of life and skeletal-related events, response, response duration and survival. examination of subgroups (high dose treatment with stem cell support vs. conventional therapy, stage III vs. Stage I / II), and other quality of life parameters assessed from the quality of life questionnaire.

Design: Within four weeks after start of chemotherapy and after completing the life quality questionnaire randomly assigned patients to 30 and 90 mg pamidronate given as 2½ hours infusion every month. The dosage is blinded, e.g. through local pharmacy. Through contact to 'Copenhagen Trial Unit' randomization is made by minimisation principle on the basis of stratification variables: high dose treatment with stem cell support vs. conventional chemotherapy, WHO performance status (0 / I vs. ≥ 2) + / - thalidomide and β_2 -microglobulin (high, non-elevated, or not known).

Delivery and settlement of investigational drug: Amgros a / s Denmark transmit medication for use to the participating clinics.

Study duration: Inclusion of patients continues until there are included 500 patients expected in about two years, and follow-up period continues until all patients have been followed for at least 36 months, ie. Total duration of approx. five years.

Data recording is done at inclusion and then by submission every six months or in case of "serious adverse" events (SAE) or death, whereas quality of life questionnaires (QLQs) are sent directly to patients for completion each 3de months with one subordination of non-response.

Interim analysis: A Monitoring and Safety Committee consisting of haematologist, statistician, clinical trial expert assesses primary efficacy and serious adverse events (SAE) the first time after the first 200 patients have been followed for at least six months.

1. BACKGROUND

Multiple myeloma is characterized by an infiltration and proliferation of malignant plasma cells in bone marrow that is hematopoietic active. This leads to a general weakening of the bones (osteoporosis) and in most patients a formation of osteolytic lesions at risk for spontaneous fractures, hypercalcemia and the development of renal failure. The course of the disease is characterized by pain, fatigue and impaired physical function (1).

Response to cytotoxic agents and thereby the possibility of physical training may to some extent delay the progression of skeletal disease in multiple myeloma. However, only about half of the patients achieve an objective response to treatment and complete response is rare by conventional treatment. In most cases bone disease develops further even in phases with apparently good disease control. Healing of skeletal lesions occurs very rarely at the usual chemotherapy. It is uncertain whether this is more frequent in patients who achieve complete response.

For several years ago it has been shown that skeletal destruction in multiple myeloma linked with an imbalance between bone degradation and bone formation (2). The malignant plasma cells produce cytokines that stimulate osteoclasts to proliferation and increased bone resorption, and also inhibited osteoblasts bone formation (3). Conversely stromacells in the bone marrow including osteoclaster and osteoblasts unleashes cytokines that stimulate myeloma cells to proliferate and inhibit apoptosis via the so-called paracrine loop (4).

In recent years, there has developed a new class of drugs, bisphosphonates, which are able to inhibit osteoclast activity (5). They have shown good efficacy in hypercalcemia caused by malignant skeletal disease (6). It was therefore logic to investigate whether these drugs can inhibit the development of skeletal disease in multiple myeloma. In a large placebo-controlled study with etidronate given orally as a supplement to standard chemotherapy this treatment had no effect on skeletal pain, reduction of body height or frequency of pathological fractures and hypercalcemia (7). There was no significant difference in survival between the two groups (7).

In a Finnish placebo-controlled study with orally clodronate 2400 mg daily for 24 months (8), there was a smaller proportion among the actively treated than in placebo-treated patients who showed progression of osteolytic bone lesions during a 24 month period (12 vs. 24 %, $p = 0.03$). However, there was no statistically significant difference between the groups regarding pain score or consumption of

analgesics, and it is difficult to estimate how much benefit the patients in fact had from the treatment. There was no difference in survival between the groups.

In a similar English clodronate study (9), where the dose was 1600 mg per day orally was found statistically significant difference between the groups with respect to back pain at 24 months. The prevalence of poor performance status was greater among patients in the placebo group (30% versus 18.3%, $p < 0.025$). There were also among placebo-treated patients significantly more non-vertebral fractures (36 versus 20, $p = 0.025$) and vertebral fractures (60 v 41, $p < 0.001$). Furthermore a reduced odds of dying among patients without vertebral fractures at the time of diagnosis, treated with clodronat (odds ratio 0.64, $p = 0.05$) was indicated, but this was the result from a retrospective subgroup analysis. The difference between the two patient groups appeared to increase with time (9).

In a Scandinavian study of oral pamidronate the incidence of "skeletal related events" (number of osteolytic lesions, fractures and cases in need of skeletal surgery) was less in the pamidronate group than in the placebo group (10) The need for radiotherapy and number of episodes of hypercalcemia were also lower in the actively treated group. However, none of the differences statistically significant, although the reduction of body height was significantly less in pamidronatgruppen ($p = 0.02$) and there were significant fewer episodes of severe pain among pamidronate-treated patients ($p = 0.02$). A probable reason why it has only been possible to detect limited efficacy of oral bisfosfonatbehandling is a low absorption of the drug (1-2%). There has therefore attached great interest to a study of the efficacy of intravenous pamidronate, which is conducted by a multicenter study in the U.S., Canada, Australia and New Zealand (11). 392 patients with stage III multiple myeloma and at least one osteolytic lesion were randomized to 90 mg pamidronate or placebo as a 4-hour infusion every 4 weeks for 9 months in connection with conventional cytotoxic treatment. Patients were stratified according to whether this was the first or second line treatment. The proportion of patients who had 'skeletal related events' (pathological fracture, irradiation or surgery of bones and compression of corpora in the spine) was significantly lower in treatment than in the control group (24 vs. 41%, $p < 0.001$). The patients' physical function (ECOG performance status) and quality of life (Spitzer index) was assessed by the treating physician every 4 weeks. At the final evaluation after 9 months of treatment compared to the start of treatment there was found an average worsening of pain, performance status and quality of life and an increased consumption of analgesics in the placebo group, while the pamidronate-treated patients reported less pain than at baseline and unchanged status of the other variables. Only at a time (7 months) there was no statistically significant difference ($p < 0.05$) between the two groups. In the original article (11) has not reported any significant difference in survival between the groups. In a subsequent follow-up after 21 months of treatment (12) it is highlighted that in stratum 2 (previously treated patients) gave a difference in survival after adjustment for imbalances in the distribution of serum β -2 microglobulin and ECOG performance status (20.6 vs. 14.1 months, $p = 0.04$). The treatment had few side effects. By this analysis, there was no more significant difference in number of pathological fractures (31% vs. 37%, $p = 0.21$) or number of radiation treatments (25% vs. 34%, $p = 0.06$). For any skeleton episode this study still shows a statistically significant effect of intravenous pamidronate treatment (38% vs. 51%, $p = 0.016$) The study is conducted on a selected patient population. Only stage III patients with at least one osteolytic lesion is in the study. From 88

hematology centers were in a three-year period included average only 1.5 patients per. center per year. The results from this study can not readily be generalized to all multiple myeloma patients. Recently, a European placebo-controlled multicenter study with a more potent bisphosphonate, ibandronate (2 mg intravenously monthly), could not demonstrate significant reduction of "skeletal related events", but indicated a trend towards longer survival in ibandronat group (33 vs. 28 months, non-significant) (13).

The conclusion of the present studies is that for some patient groups it appears that intravenous pamidronate and to some degree oral clodronat have effect on skeletal morbidity but the optimal dose for these bisphosphonates remains unresolved and there are studies ongoing to assess the safety and efficacy of pamidronate up to 180 mg two times per month (14). While there is widespread consensus that bisphosphonates have effects on skeletal disease in multiple myeloma the dosage and size of the population who should be treated remains unclear (15).

In light of these various clinical studies (9,12,13) which suggest a prolonged survival of multiple myeloma patients treated with bisphosphonates, it has been considered whether this effect alone is secondary to the reduced skeletmorbiditet or whether there is a direct antimyelomeffekt . *In vitro* studies have shown that especially the highly potent bisphosphonates (pamidronate, risendronate and zoledronate) can induce apoptosis and reduced proliferation of myeloma cell lines (16.17) and of freshly isolated myeloma cells from three patients with multiple myeloma (17).

Several newer and ever more potent bisphosphonates are developed and have been or are being tested in various clinical situations: alendronate, risendronat and ibandronat. In a rat model the relative equipotent doses have been assessed to 1: 2: 10: 50: 500 for ibandronat: risendronat: alendronate: pamidronate: clodronat (18). While pamidronate requires relatively long infusion time, other more potent bisphosphonates as ibandronat been administered by infusion over two hours at dosages up to 6 mg (19.20) and as a bolus up to 3 mg (21). For ibandronat treatment of hypercalcemia in 173 patients with malignant diseases (19) there were relatively few serious side effects related to ibandronat: a case of thrombocytopenia (WHO grade III), one case of nausea (WHO grade II) and one case with fever (WHO grade III). In addition, 16 patients had less serious side effects (fever (n = 10), asymptomatic hypocalcemia (n = 4), oesophagitis (n = 1) and elevated liver enzymes (n = 1)) For pamidronate the requirements for the infusion time has also changed so for routine i multiple clinics the infusion of 90 mg is 2 to 3 hours. In Norway, it is recommended to observe a maximum infusion rate of 60 mg of pamidronate per hour. From Novartis a/s it is reported that at doses of 180 mg there have been observed an increased nephrotoxicity in terms of development of glomerulosclerose (Jim Berenson personal communication).

The gain by giving bisphosphonates to prevent the development of skeletal disease in all patients with newly discovered multiple myeloma may not be inferred from the available results. However, the entend of bisphosphonate treatment for multiple myeloma as large and generally recommended (22) that it would be difficult to conduct a new placebo-controlled study for stage III patients with radiological skeletal changes in order to demonstrate its value. Although a beneficial effect of

pamidronate (and clodronate) treatment in multiple myeloma is likely, the optimal dosage and the overall cost-utility efficacy is undetermined, and the impact on patients' quality of life is insufficiently elucidated.

It is therefore indicated to conduct a dose-efficacy study with a population based material for the following issues:

1. Which bisphosphonate dosing is optimal? Can the same effect is achieved with one third of the dose and cost instead of the standard dose of 90 mg?
2. Does bisphosphonate therapy improves patients' quality of life? The main purpose of bisfosfonatbehandlingen is to reduce and slow the progression of the skeletal disease. Therefor the patients' quality of life should be a primary endpoint. NMSG has in a previous study showed that the questionnaire developed by EORTCs group on quality of life research, EORTC QLQ-C30, has a high reliability and validity of multiple myeloma (1). This study also showed that patients at diagnosis have significantly impaired quality of life, especially physical function, pain and fatigue. Response to the primary therapy with melphalan and prednisone leads to a significant improvement in quality of life parameters. The questionnaire was also suitable for comparing the quality of life between groups of patients who were randomized to standard care or additional treatment with interferon α -2b (23).
3. How much is the prize that may be achieved in terms of improved quality of life and possibly survival? The price for a year iv bisfosfonate treatment eg pamidronate treatment with 90 mg IV every 4 We want to make a health-economic (cost-utility) analysis of treatment outcome, so that bisphosphonate treatment of different categories multiple myeloma patients can be assessed relative to other uses of resources within the health sector. Using prospectively collected data on quality of life and consumption of resources, we will calculate the price of a winning life quality-adjusted life years (Quality Adjusted Life Year, QALY). QALY analysis can be made even if the potential benefit of treatment is a pure life quality and no prolongation of survival.
4. Which patients with newly diagnosed multiple myeloma benefit of prophylactic bisphosphonate treatment? The available data are all from patients who have undergone conventional chemotherapy. Today high dose treatment with autologous stem cell transplantation is an established

treatment for younger myeloma patients (24.25). It is unknown what benefit patients receiving high dose treatment with autologous stem cell injection could obtain from bisphosphonate treatment. In addition to analysis of the entire patient material a comparison of three doses within following two subgroups must therefore be performed:

- patients treated with conventional chemotherapy and
- patients who are planned to receive high dose treatment with stem cell support.

OBJECTIVES

Primary endpoint:

To determine which of two doses of intravenous bisphosphonate that has the best effect on quality of life assessed by physical functioning as measured by EORTC QLQ-C30.

Secondary endpoints:

investigate the effect of two doses of intravenous bisphosphonate treatment on

- a. objectively skeletal related events (spontaneous fractures, new compression of vertebrae, new osteolytic lesions, need for radiotherapy or surgery, unequivocal progression of previously recognized osteolytic lesions).
- b. a cost-utility analysis of the possible benefits for quality of life and skeletal-related events
- c. any differences in subgroups (conventional chemotherapy vs. high dose treatment with stem cell support, stage III vs. stage I / II).
- d. response, response duration and survival
- e. quality of life rated by fatigue and pain.

3. STATISTICAL IMPLICATIONS

Quality of life parameters:

In a previous study (26), we have shown that a low self-reported function is associated with a poor prognosis. It is therefore a measure of actual treatment with bisphosphonates to increase physical disability on a scale from 0-100. For patients who after 12 months of treatment had achieved objective response to treatment with melphalan and prednisone (MP) (minor response or better), the proportion of patients with physical disability ≤ 40 was 17% and for non-responders 46%. For the entire group of MP-treated patients, the proportion 26%. A significant difference in the quality of life between two groups that should be detectable with high probability in

the study corresponds to the reduction of the proportion of patients with physical disability ≤ 40 from 26% (all MP group) to 17% (responders). With this based calculation the required patient number for data at that (ordinal) measuring levels according to Campbell et al (27) to 211 evaluable after 12 months in each of the two groups. The key calculation is an α at 0.05 and a β of 0.10. Therefore it is planned to include 250 patients in each dose group, taking into account mortality during the first 12 months of treatment.

The final analysis of physical function as primary endpoints will after 12 months of treatment be performed on the subordinate categorical data on physical function.

In subsequent analysis after treatment completion of the plan (ie at least 3 years of treatment) will physical functioning also be analyzed as longitudinal data by the General Estimating Equations Analysis (GEE) or - if this is negated - by Standardized Area Under the Curve () analysis which for each patient calculated an average measure of physical functioning over follow-up, divided by the length of patient follow-up.

The primary life-quality endpoint will then be physical function. As a secondary life-quality endpoints, we will compare the groups with regard to pain and fatigue, also are important problems for multiple myeloma patients (1), and bisphosphonates likely to have analgesic effect which could be dose dependent. The other quality of life data will be used in other exploratory analysis.

The 500 randomized patients does not give a sufficient test power to conduct a subgroup analyzes of the quality of life within the subgroup receiving high-dose therapy and stem cell transplantation or for comparing the groups with and without osteolytic lesions. These subgroup analyzes must therefore be explorative in terms of quality of life.

Skeletal morbidity:

In the previous Scandinavian study of oral pamidronate (10), the median time to first skeletal related event (SRE, skeletal related event) approx. while the study of Berenson et al (11,12), which enrolled patients with stage III and at least one osteolytic focus of which approx. half of the patients had received prior chemotherapy, the median time to first SRE 15 and 21 months in placebo and actively treated group, respectively. The inclusion of newly discovered multiple myeloma patients without osteolytic foci or lower stages the estimated median time to first SRE is thought to be longer (about 18 months).

Randomization of 500 patients allows a proof of six month's extension of the median time to first SRE conditional bisphosphonate treatment at each dose level with an inclusion time of 24 months and an observation time of at least 36 months when taken with a mortality of approx. 60% over a median observation time of four years. (Level of significance (α): 0.05 and β 0.20, but without regard to who is one of several secondary 'endpoint').

To investigate the value of other endpoints for skeletal morbidity desired eksplorative for later skeletal events either as equal events or as a skeletal event score:

Event type	Scores
<i>Pathological fracture</i>	3
<i>Radiation or surgical treatment of fracture threaten focus</i>	3
<i>Palliative radiotherapy for pain</i>	2
<i>New symptomatic foci outside spine</i>	2
<i>Several new foci in the spine (including compression fractures)</i>	2
<i>Single focus in the spine (including kompressionfraktur)</i>	1

However, there is no data available which allows a sizing calculation for these statistical parameters. However, the application of even later events than first SRE is considered only to increase the statistical power.

Survival: The size of the study population is not considered to be sufficiently large to demonstrate a prolongation of survival by bisphosphonate treatment within a period of 36 months. Therefore, the possibility of extending the observation period of at least 50 months to assess the effect on survival.

4. DESIGN

The study is conducted as a randomized, double-blind, dose-effect, clinically controlled study.

While Novartis a/s has not been able to deliver projects medication blind, and it is not possible to make a secondary blinding as a secondary blinding of 'vials' is not possible when the normal requirements for drug manufacturing should be respected, the planned blinding is implemented through the appointment one or two people in every department from a locked cupboard / box mixes the study drug in the randomized dose, or the blinding is carried out by local pharmacy. However, the treating physician, nurse and patient will not be aware of the dose until after the study is completed.

Since there is full support in NMSG to complete the study as outlined, each clinic in collaboration with the regional coordinators will ensure that blinding is as efficient as possible.

The expected inclusion rate of approx. 25 patients per months, ie. a total enrollment time around. wo years and at least 36 months' follow-up results in a total study time around. ive years.

5. PATIENT SELECTION

Inclusion Criteria for:

General: All patients regardless of age, with newly diagnosed multiple myeloma that require treatment regardless of stage within the NMSG's area in Denmark, Norway and Sweden, can be included.

Diagnostic Criteria: NMSG's criteria (see ANNEX I)

Chemotherapy: Initial Treatment with MP: melphalan 0.25 mg / kg body weight orally daily half hour before breakfast on DAY 1-4 predniso(lo)n 100 mg orally daily (or 2 mg / kg / day) DAY 1-4 repeated at 4-6 week intervals, or high dose treatment with peripheral stem cell support (PSCT) according to NMSG 07/98, and any subsequent highdose protocols under NMSG; therapy at treatment failure / relapse is chosen freely.

Any protocols that evaluate thalidomide during primary treatment or therapy failure, is allowed when ensured a uniform random allocation to treatment arms.

Response Criteria: As in NMSG 7 / 98 (see Annex I).

Exclusion Criteria:

- a. Patients with expected life spans of less than 3 months
- b. Patients with simultaneous second active malignancy.
- c. Patients who have been treated with bisphosphonates for more than three months within the last six months (ie, treatment for hypercalcemia is allowed).
- d. Patients at the start of treatment according to the protocol not later than four weeks after the chemotherapy continue to have S-creatinine > 400 µmol / l.
- e. Patients where monthly injection treatment is not deemed feasible for technical or practical reasons.
- f. Patients who do not wish to participate in the study.

6. INCLUSION AND RANDOMIZATION (see also ANNEX VI)

Randomization must be no later than four weeks after the first chemotherapy. Before randomization patients must have completed the first quality of life questionnaire.

Registration and randomization is done via telephone to Copenhagen Trial Unit (telephone: +45 35457171 Jette Pedersen, Nina Frydendakk +45 35457170 or +45 35457169 Dimitrinca Nikolova) (Checklist). There will be used stratified randomization by minimization principle (28) with the centers that use high dose treatment, organized on randomization of one MP block and a high dose block. Before randomization carried out, the investigator verifies that patients:

- a. Meets diagnostic criteria.
- b. Has been provided and completed quality of life form.
- c. Not covered by some of the exclusion criteria.
- d. Have given written informed consent.
- e. About planned high dose chemotherapy or conventional chemotherapy usually MP (*stratification variabel*)
- f. WHO performance status should be available (*stratification variabel*)
- g. Possible participation of thalidomide protocol (*stratification variabel*)
- h. β -2-microglobulin concentration, if available (*stratification variabel*)

Quality of Life Form is sent with a copy of the checklist to the Secretariat for Quality of Life and Health Economics in Oslo with the exact name and address of the patient, and a copy of the checklist is sent to regional coordinator.

Copenhagen Trial Unit sends by e-mail (or possibly via fax) to Amgros a/s information on the patient's name, address, randomization number, what dose and what the clinic and hospital the study drug should be sent to, and send in an ongoing list of patient names, addresses, randomiseringsnummer, clinic, but without specifying the dose to the Central Secretariat and the Quality of Life Secretariat in Oslo. Amgros a/s sends labelled product to the person at the clinic or related hospital pharmacist who is responsible for mixing the product and thus the blinding. Amgros a/s will ensure regular supply and settlement on the basis of a list of blinding and billing responsible person in each clinic.

In Denmark and Sweden medicine is sent individually to the specified address, while the medicine to be sent to Norway will be delivered to once a week. Consignments to Norway are packaged and addressed to the individual patient at the hospital. Besides the patient's name is randomiseringsnummer indicated. If Amgros does not receive notification that the patient is excluded, they will send study drug subsequently every 6 month medicine for this patient until the investigation is completed after three years.

For recipients in Sweden must Amgros a/s to know the recipient's SE-nr. for shipment can be sent without VAT.

In Norway, have sent a copy of the Norwegian authorities' approval of the clinical examination.

Following notification from CTU about patient number in connection with the randomization the individual clinic gives information of patient number, patient name and social security number to the responsible for preparing the blinded study drug at the clinic / hospital. The blinding responsible receives from Amgros the product packed with information on dosage and patient number. In light of this information, labeled medication to the patient's name, number and kept a list of patients and dose. Whoever is responsible for the blinding and preparation of medicine have to keep a list of what dose the patient is randomized to, and shall ensure that the mixed medicine is labelled with patient number and patient identification possible with name and birth data before delivery to the treating doctor /clinic. The person who is responsible for mixing and blinding may not otherwise be involved in study implementation.

If it is deemed necessary to know the dose (unexpected side effects and complications that are considered so serious that postpone of therapy alone is not considered sound) can the blinding be abolished after contact by phone to CTU - in this case the patient will be excluded for the remainder of the treatment

Patients not included, either because they do not want it or because of exclusion criteria also exclude participation, in writing and orally be queried whether they accept the registration, in line with previous NMSG protocols to characterize both the included as the negative population.

7. PATIENT INFORMATION

All patients offered to enter the study shall be informed both orally and in writing (see Annex II) concerning the clinical study presentations and objective. The patient gives both verbal as written consent.

As indicated above, provided patient information on registration for non enrolled patients (see Annex III).

8. BISPHTHONATE TREATMENT

Intravenous pamidronate (Aredia[®]) 30 mg or 90 mg once monthly.

Recommended procedure for the preparation and administration: Both doses of pamidronate-substance dissolved in an ampoule with 10 ml of solvent and then mixing in 500 ml isotonic glucose (5%) (solution is stable for 12 hours) or other intravenous fluids according to local routines, labeled with patient name and randomiseringsnummer, but without specifying the dose, and is infused over 2½ hour.

Duration of treatment: at least 36 months months.

Treatment may be discontinued (or postponed) if:

- a. Adverse events require.
- b. The patient wants it.

- c. The patient within the past two weeks have had symptomatic hypercalcemia, which has required treatment with intravenous bisphosphonate.

9. INVESTIGATIONS AND REPORTING

a) At the time of diagnosis carried out the studies necessary to establish the diagnosis. There must be X-ray: cranium, spine, pelvis and long bones and chest. There must be frozen 10 ml of serum and plasma from each patient at diagnosis. (Form No. 1).

X-ray examinations should be repeated after 9 months and 24 months or if there is clinical indication for it.

Moreover, only such studies as required from the clinical situation.

b) Quality of life. The precondition for participation in the project is that the patient is willing to participate in QLQ recording (as evidenced by patient information). EORTC QLQ-C30 version 3 will be used. Prior to randomization the patient completes the first schedule which is sent along with copies of the registration form on the Quality of Life Secretariat in Oslo. Subsequent questionnaires will be sent directly to the patient along with stamped return envelope every 3 months as long the observation period continues, ie. three years. If the patient does not respond to the first contact will be moved once.

c) Skeletal events. Skeletal events include pathological fractures, osteolytic foci as radiation treatment, osteolytic foci requiring surgical treatment, other newcomers or progressive symptomatic osteolytic foci. For each event type, time and therapeutic impact should be specified (Form No. 2). Moreover recorded hypercalcemia cases. For the fixed X-ray studies (after 9 and 24 months) a special form should be completed (Form No. 3).

d) Follow-up Schedule with clinical events (including adverse events according to WHO) and economic data as is required every 12th week, ie. 3de each time the patient has bisphosphonate (Form No. 2). Once every six months sent the forms in to the regional coordinator and on to the Central Secretariat in Copenhagen. Number of days in hospital, days off sick, consultations with doctor and nurse is recorded.

e) Follow-up time: minimum 36 months.

f) Serious adverse events (serious adverse event (SAE) (WHO Grade 3 or 4)) are notified to the Central Registry within 24 hours (weekdays). With a serious adverse reaction refers to any adverse events which leads to:

- life-threatening situation
- hospitalization, prolongation of an existing hospitalization, or recurrent hospital consultations for other reasons than because the myeloma disease

- '(WHO grade 4) with the exception of the predicted cytotoxic-induced granulocytopenia or thrombocytopenia that does not lead to complications in the form of serious infection or bleeding
- permanent and significant disability.

(Reported on Form No. 4).

h) Deaths are reported to the Central Registry within 24 hours on weekdays until the study is ongoing (Form No. 4). The Central Registry provides that "the Secretariat of the life quality and health economics' in Oslo immediately is notified.

10. INSURANCE MATTERS

The study is initiated by the Nordic Multiple Myeloma Study Group and conducted independently by the manufacturer. Participating patients are covered by public insurance under the applicable law in each country.

11. ETHICS

Bisphosphonate treatment of multiple myeloma patients is widespread, but no studies have been published to demonstrate the optimal dose, and the studies that have shown efficacy have used widely different active doses. Therefore, there is no data that makes it probable that the lowest dose should not be effective. Through a thorough side effect registration must be taken to ensure that there is no unforeseen side effects. The protocol allows the use of bisphosphonates in proven effective doses in case of hypercalcemia.

The study starts only when approved by the respective country or regional science ethics committees. Furthermore, the protocol approved by health authorities (in Denmark: Medicines Agency and Registry Regulators, Norway: Statens Legemiddelskontroll and Data Inspectorate and in Sweden: Läkemedelsverket).

Patients give informed consent see ANNEX II and approve the same time that frozen plasma and serum may provide a basis for analysis of factors that may influence the disease course and diagnosis.

12. THE INTERIM ANALYSIS

The outcome of the interim analysis will not be granted the study management group or the participating centres in the study unless the result can motivate a change in schedule or an earlier closure of the study. The first interim analysis is carried out after the first 200 patients have been followed for six months. If at this time is significant difference ($P < 0.001$) for physical functioning goals in life quality questionnaire, the study will be stopped. At the same time the number of 'serious adverse event' (SAE) in the two dose groups are assessed and by significant differences with the same P-value above the study can also be stopped.

Subsequent interim analyzes are decided by the safety committee assessment in light of the first analysis.

Monitoring and Safety Committee consists of Jørgen Hilden, associate professor at Copenhagen University's Institute for Biostatistik, Nis Nissen, MD. haematologist and former chef of hematological clinic, Rigshospitalet and Sjúrdur Olsen senior physician, MD., Department of Epidemiology Research, Statens Serum Institut.

The agenda for DMSK shown in Annex IV.

13. ADMINISTRATION

The participating departments are organized in the same structure as has been used in previous studies NMSG with a contact person at each hospital and a regional coordinator with responsibility for monitoring the follow-up forms.

Study the main secretariat will be in Copenhagen (*Med. Haematological Dept. L4042, Rigshospitalet, DK-2100 Copenhagen Fax: +45 35455427*). Secretariat of life quality and health economics as in previous studies in Oslo (*Office of Clinical Kreftforskning', IK 3rd floor, Ullevål hospital, N-0407 Oslo, Norway, Phone and Fax +47 22118192*).

14. SIDE PROJECTS

A proportion of patients at major hospitals will be followed by Bone densitometry and biochemical bone markers. This project also from Aarhus (Niels Abildgaard).

Patients receiving radiotherapy during the study period is recorded separately to clarify the dose and fractionation, together with an assessment of radiation effects. This project also from London (Ulla Brix Tange).

15. ECONOMY

Negotiated with Novartis Healthcare A / S, Denmark, on a discount for Aredia:

N.vnr. 194,795 Aredia 90 mg of 1,480.00 Dkr.

N.vnr. 413,864 Aredia 30 mg (x2) 930.00 Dkr.

Amgros a / s Denmark has offered to stand for the distribution and settlement with each pharmacy/clinic for 3% of purchase price. Amgros a/s settles to an average price for the two doses to achieve the least possible risk of blinding broken. Amgros a/s must be informed of the exact address of who will pay for medication for each patient. price for delivery is Dkr. and payment deadline is 14 days.

Nordic Cancer Union has initially granted 300,000 NOK to cover the expenses of the central secretariat and the secretariat for the quality of life and health economics in relation to a previously planned placebo-controlled study. It has been approved to

transferre the grant to the present dose-effect study to cover the cost of the first 12-18 months

In addition, Novartis A / S agreed to support the study of 100,000 Dkr. per academic year.

16. PUBLISHING.

He who is the head of the Central Secretariat is the first writer for a major publication with the main skeleton and quality of life parameters. Those who are looking for Quality of Life Secretariat is responsible for a more detailed analysis of quality of life data and the health economic calculations (in collaboration with a health economist). NMSG's rules for publication of general application in accordance with Vancouver framework.

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ANNEX I

Diagnostic criteria:

- A. Monoclonal immunoglobulin (M component) in serum of type IgG > 30 g / l of type IgA > 20 g / l of type IgD or IgE regardless of concentration and / or excretion of M-component in the urine of type κ or λ > 1 g/24 hours.
- B. M-component in serum and / or urine at concentrations lower than those mentioned under 'A'.
- C. 10% or more plasma cells in knoglemarvsaspirat or plasmocytose in biopsy of bone or soft tissue tumor.
- D. Osteolytic skeletdestruktioner.

To diagnose multiple myeloma requires one of the following combinations: A + C, A + D, or B + C + D (or non-secretory myeloma C + D).

Response Criteria

(Partial) response (PR):

Reduction of M component in serum for $\leq 50\%$ of output value and reduction of M component in urine ≤ 0.2 g/24 hours. Concomitant clinical improvement in pain-freedom, increasing hemoglobin (≥ 100

g / l ≥ 6.2 mmol / l) and normalization of hypercalcemia, while creatinine may not rise.

If the M-component is small so the reduction is difficult to estimate, may a reduction of the number of plasma cells in bone marrow smear together with the other criteria to evaluate response.

Complete response (CR):

No identifiable M component in serum or urine by conventional methodology. Normalised marrow examination (<5% plasma cells).

Minor response (MR):

Reduction of M component in serum for $\leq 75\%$ but not $\leq 50\%$ of output value and reduction of M component in urine to $\leq 50\%$ but not to ≤ 0.2 g/24 hours. Simultaneous clinical improvement with pain freedom, increasing hemoglobin (≥ 100 g / l ≥ 6.2 mmol / l) and normalization of hypercalcemia.

Plateau Phase

After obtaining a kind of response (partial, minor or full) and less than 10% 's variation of three consecutive measurements of M component in serum or 3 measurements of M-component in urine ≤ 0.2 g / 24 hours.

Non response (NR):

When the criteria for CR, PR or MR are not met.

Relapse:

Patients who after obtaining responses at two or three consecutive measurements show an increase in M component in serum $> 25\%$ (at least to 10 g / l) or increase of M component in urine for > 1 g/24 hours, or other unequivocal signs of disease progression (hypercalcaemia, progressive osteolytic foci in the skeleton, or the presence of plasmocytom or unambiguous increase in the number of plasma cells in bone marrow).

Therapy failure:

Patients taking on treatment with chemotherapy and who for at least two consecutive measurements at least 2 weeks apart shows an increase in M component in serum $> 25\%$ (less than 10 g / l) or increase of M component in urine for > 1 g/24 hours , or other

unequivocal signs of disease progression (hypercalcaemia, progressive osteolytic foci of the skeleton, or the presence of plasmocytom or unambiguous increase in the number of plasma cells in bone marrow).

II

PATIENT INFORMATION

We would like to ask if you would like to participate in a Nordic research project on treatment of multiple myeloma. The purpose of the project and what your participation will imply is described below.

We want to stress that your participation is entirely voluntary and you are entitled to leave the study whenever you wantou have given yours written consent.

that you suffer from the disease multiple myeloma. . The most important result of the disease is loss of calcium from the bones leading to weakness and pain from the skeleton. Moreover the disease can lead to anaemia, increase the risk of infections and induce some degree of renal failure.

Multiple myeloma is treated with chemotherapy that can stop the progression of the disease..

During the recent there have been developed new drugs, bisphosphonates, that seem to delay the development of bone destructions of various malignant skeletal diseases. bRecent studies suggest that these drugs have the power to delay the skeletal disease in multiple myeloma.

in patients diagnosed with myeloma in the Nordic countries. All patients will be treated with chemotherapy according to present guidelines.

anonymously. Therefore you give your consent that the Nordic investigators and the heakth authorities made read your files for up to 15 years after the study has been closed.

Information given by:

:

Patient Signature

.....

: Senior physician Peter Gimsing

L, Rigshospitalet

DK-2100 Copenhagen for Ö

Senior physician

Medicinska Kliniken, University Hospital MAS

205 02 Malmö, Sweden, Tel. 040 33 10 00

Norway: Professor Finn Wisloff,

University Hospital, Ullevål, Oslo

Responsible doctor for the study at your clinic is:

.....

Address

Phone

Namn Address Phone

III

Patient information for patients not included in the study.

Since this planned part was never done this is not translated.

ANNEX IV

and Safety Committee (DMSK)

The Committee consists of:

Jørgen Hilden, associate professor at Copenhagen University's Institute for Biostatistik

Nissen, MD. Haematologist, and former klinikchef of hematology clinic, Rigshospitalet

Sjúrður Olsen senior physician, MD., Department of Epidemiology Research, Statens Serum Institut.

DMSK

1. *First interim analysis.* After the first 200 patients have been followed about board receives from Copenhagen Trial unit statistically processed results for 'primary endpoint. *"If this time is significant difference ($P < 0.001$) for physical function as measured by life quality questionnaire recommend DMSK study steering group to experiment ends.*
2. At the same time sent a list of notified SAE and deaths in the two dose groups (30 and 90 mg pamidronate)
3. DMSK prepare a report to the Steering Group, which without giving details of the analysis recommends steering committee
 - a. To set the studio where they point. If specified conditions are met, or if DMSK estimates that registered SAE and death have a nature that it is unethical to continue
 - b. That study continues, but that more interim analyzes are performed.
 - c. The study will continue until enrollment of the planned number of patients and the subsequent follow up under the protocol is reached.

At any subsequent assessments follow the same principles as the first interim analysis.

It is up to the steering committee to assess whether new published studies bring to the data that makes it unethical to continue the study.

ANNEX V

OVERVIEW OF STUDIES

	BEFORE	MONTH 3 and 6	MONTH 9	MONTH 12,15,18,21	MONTH 24	EVERY MONTH 3rd
Quality of Life Schedule	O	O	O	O	O	O
B-hemoglobin	O	O	O	O	O	O
B-leukocytes	O	O	O	O	O	O
B-neutrophils	O	O	O	O	O	O
B-thrombocytes	O	O	O	O	O	O
S-M-component type	O					
S-M-component, g / l	O	O	O	O	O	O
U-M-component type	O					
U-M component g/24h	O	O	O	O	O	O
S-creatinine	O	O	O	O	O	O
S-albumin	O	O	O	O	O	O
S-calcium (alb-korr.) α	O	O	O	O	O	O
S-calcium (ion) α	O	O	O	O	O	O
S-LDH	O	O	O	O	O	O
S-sodium	O	O	O	O	O	O
S-potassium	O	O	O	O	O	O
B / P-glucose	O	O	O	O	O	O
	O					
S-C-reactive protein (CRP)	O					
	O					
S-alkaline-phosphatase	O					
S-bilirubin	O					
P-APTT	O					
INR	O					
10 ML SERUM	O					
	O					
Bone marrow aspiration	O	By CR, progression, or every three months by non-secretory myeloma				
Weight	O					
Height	O	O	O	O	O	O
Performance status	O	O	O	O	O	O
X-ray of the cranium, thoracic, lumbar totalizing, pelvis, femora, humerus	O		O		O	
Skeletal Events	O	O	O	O	O	O
Side effects (WHO)	O	O	O	O	O	O
Number of days hospitalized		O	O	O	O	O
Number of days on sick leave		O	O	O	O	O
Number of doctor visits		O	O	O	O	O
Number of nursing visits		O	O	O	O	O
Disease status		O	O	O	O	O

α Either alb.corrected calcium (total calcium + 0.02 (40 - S-albumin (g / l))) or ionized calcium

ANNEX VI

PRACTICAL GUIDE FOR INCLUSION OF NEW A PATIENT AND TREATMENT START

After obtained informed consent and the patient has completed quality of life scale:

1. Checklist is completed including statificeringsvariable (Performance status 0 / 1 vs. ≥ 2 , planned HD vs conventional chemotherapy, planned thlidomide treatlent, β -2-microglobulin <2.6 mg / l vs. ≥ 2.6 mg / l vs. not *known*)
2. Copenhagen Trial Unit (CTU) is contacted by telephone (Monday to Friday. 9-16) (+45) 35457171 (Jette Pedersen), (+45) 35457170 (Nina Frydendall) or (+45) 35457169 (Dimitrinca Nikolova) and will assign a randomisation number.
3. Quality of Life Questionnaire and a copy of the checklist is sent to the Secretariat of the Quality of Life and Health Economics in Oslo with precise indication of the patient's name and address.
4. Checklist sent to the regional coordinator.
5. CTU assign a randomisation number and allocate the notifying doctor / person a pin code to use in future reviews.
6. CTU mails by e-mail (or send by Fax) information to Amgros a / s indicating randomisation number, dose, and the clinic / hospital medicine to be sent.
7. CTU sends current overview of randomisation number, patient name, address, birth date and clinic for Central Secretariat and the Secretariat of the Quality of Life and Health Economy in Oslo.
8. Amgros a / s transmit medication for six months consumption labelled with randomisation number, patient name and dosage to the person responsible for the blinding at each clinic
9. *In Denmark and Sweden the medicine is sent directly to the person responsible for the blinding at each clinic (NB! Departments in Sweden is to inform the recipient's VAT number since otherwise payable VAT (25%))*

10. *Norway is sent medicine via 'Norwegian Medical Depot'*
11. Amgros a / s then sends medicine to the patient every 6 months unless previously been told that the patient has left the studio.
12. Amgros a / s send invoice to the person responsible in each clinic to be finalized within 14 days after delivery (Dkr. 5951.70 for six doses, including delivery).
13. Notifying department shall within four weeks send notification form to the regional coordinator who, upon examination of the form send a copy to the Central Secretariat in Copenhagen.
14. Regularly every 6 months is sent follow-up forms to the patient to the regional coordinator who, after examining the form is sent a copy to the Central Secretariat in Copenhagen.
15. Secretariat of the Quality of Life and Health Economics in Oslo, each 3de month a new questionnaire directly to the patient's address.
16. By death or expulsion from the studio is given immediately (within a day everyday) message to the central secretariat in order to avoid delivery of unnecessary drugs and deployment of Quality of Life form for the deceased.