

NEM[®] Brand Eggshell Membrane Effective in the Treatment of Pain Associated with Knee and Hip Osteoarthritis: Results from a Six Center, Open Label German Clinical Study

Ulrich Danesch^{1*}, Marion Seybold¹, Reiner Rittinghausen¹, Walter Treibel² and Norman Bitterlich³

¹Weber and Weber GmbH and Co. KG, Biological Medicinal Products, Herrschinger Str. 33, D-82266 Inning/Ammersee, Germany

²Orthopedic Practice, Maxhofstr. 9a, 81475 Munich, Germany

³Medizin and Service GmbH, Boettcherstr. 10, 09117 Chemnitz, Germany

Abstract

Objective: NEM[®] brand eggshell membrane is a novel dietary supplement ingredient that contains naturally occurring glycosaminoglycans and proteins essential for maintaining healthy joints. A six center, open label clinical study was conducted to evaluate the efficacy and safety of NEM[®] as a treatment for pain and inflexibility associated with osteoarthritis of the knee and/or hip in a European population.

Methods: Forty-four subjects received oral NEM[®] 500 mg once daily for eight weeks. The primary outcome measure was to evaluate the mean effectiveness of NEM[®] in relieving general pain associated with moderate osteoarthritis of the knee and/or hip at 10,30 and 60 days utilizing a 10-question abbreviated questionnaire based on the WOMAC osteoarthritis questionnaire.

Results: Supplementation with NEM[®] produced a significant treatment response from baseline at 10 days (Q1-6 and Q9) (8.6% to 18.1% improvement) and at 30 and 60 days for all nine pain-related questions evaluated (22.4% to 35.6% improvement) and at 30 and 60 days for stiffness (Q10)(27.4% to 29.3% improvement). In a Patient's Global Assessment, greater than 59% of patients rated the efficacy of NEM[®] as good or very good following 60 days of supplementation. Physicians also rated the treatment effective in subjects, with greater than 75% having moderate or significant improvement from baseline after 60 days. There were no serious adverse events reported during the study and the treatment was reported to be well tolerated.

Conclusions: Supplementation with NEM[®] significantly reduced pain, both rapidly (10 days) and continuously (60 days) demonstrating that it is a safe and effective therapeutic option for the treatment of pain associated with osteoarthritis of the knee and/or hip. Results from previous clinical studies on NEM[®] can likely be extended to the broader European population.

Keywords: Knee, Hip, Osteoarthritis, Eggshell membrane, NEM, Dietary supplement, Glycosaminoglycans

Introduction

Estimates of the prevalence of osteoarthritis (OA) in European populations vary widely, however a recent study [1] from a region in Spain places the prevalence of knee OA at 12.2% and that of hip OA at 7.4%. The pain associated with these maladies can be quite debilitating and few treatment options exist outside of easing symptoms. This usually involves the use of analgesics (i.e. acetaminophen, oxycodone, propoxyphene) or non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. ibuprofen, diclofenac, celecoxib), alone or in combination. Most of these treatments have shown limited effectiveness in randomized controlled clinical trials (RCTs) [2-5] or are known to have significant and sometimes severe side effects. NEM[®] brand eggshell membrane has previously demonstrated good efficacy in relieving pain and stiffness associated with OA of the knee in an RCT [6] and has shown similar efficacy in limited trials for other affected joints [7].

Eggshell membrane is primarily composed of fibrous proteins such as Collagen Type I [8]. However, eggshell membranes have also been shown to contain other bioactive components, namely glycosaminoglycans (i.e. dermatan sulfate, chondroitin sulfate and hyaluronic acid and keratan sulfate) [9-11]. A number of these constituents have been shown previously to be beneficial in the treatment of OA [12,13]. Eggshell membrane itself has been shown both *in vitro* [14] and *in vivo* [15] to reduce various pro-inflammatory

cytokines, including interleukin-1 beta (IL-1 β) and tumor necrosis factor alpha (TNF- α), two primary mediators of inflammation. A U.S. company, ESM Technologies, LLC (Carthage, MO USA), has developed methods to efficiently and effectively separate eggshell membrane from eggshells on a commercial metric-ton scale. The isolated membrane is then partially hydrolyzed using a proprietary process and dry-blended to produce NEM[®] brand eggshell membrane. Compositional analysis of NEM[®] conducted by the manufacturer has identified a high content of protein and moderate quantities of glucosamine (up to 1% by dry weight), chondroitin sulfate (up to 1%), hyaluronic acid (up to 2%), and collagen (Type I, up to 5%).

The multi-center trial reported herein was designed to evaluate the acceptability of this natural arthritis treatment with European orthopedic surgeons and patients. Success of this trial would also

***Corresponding author:** Dr. Ulrich Danesch, Weber & Weber GmbH & Co. KG, Biological Medicinal Products, Herrschinger Str. 33, D-82266 Inning/Ammersee, Germany, Tel: +49-081439270; E-mail: Danesch@weber-weber.net

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validate the extension of the body of clinical evidence for NEM® from the United States to a European population. Therefore, a 2-month open-label study was conducted at six different clinical sites throughout Germany to evaluate the efficacy and tolerability of NEM® for the relief of the pain and discomfort associated with osteoarthritis of the knee and/or hip.

Materials and Methods

Study design

The study was conducted according to a prospective, multi-center, open label design and was conducted in Germany in accordance with the International Conference on Harmonization guideline for the principles of Good Clinical Practice (ICH E6) and the Declaration of Helsinki to ensure protection of human subjects. Patients provided their written informed consent to participate. Neither the clinical investigators nor the patients were blinded to treatment (open label design). Treatment consisted once daily orally of Atrosia® (Weber and Weber, GmbH and Co. KG, Germany) providing 500 mg of NEM® in vegetarian capsules that were stored in closed containers at ambient temperature. Clinic visits were scheduled for subjects at study initiation and at 60 days following the onset of treatment. Treatment compliance was checked at clinic visits by patient interview and by counting the number of unused doses of the study medications. Analgesics (i.e. acetaminophen) were allowed for rescue pain relief. However, subjects recorded the time and amount of analgesic taken in patient diaries so that overall analgesic use could be evaluated as part of the study.

Patients

All subjects 18 years of age or older who were seeking relief of mild to moderate pain due to osteoarthritis of the knee and/or hip were considered for enrollment in the study. In order to be eligible, subjects must have had moderate persistent pain in the knee and/or hip associated with osteoarthritis and must have had baseline scores within the range of 4-7 on the first three questions dealing with joint pain. Subjects that were currently taking analgesic medications or NSAIDs every day, currently taking glucosamine, chondroitin sulfate, MSM, or collagen were ineligible to participate in the study. Patients were excluded if they were currently receiving remission-inducing drugs such as methotrexate or immunosuppressive medications or had received them within the past 3 months. Other exclusionary criteria were: a known allergy to eggs or egg products, or pregnant or breastfeeding women. Subjects participating in any other research study involving an investigational product (drug, device, or biologic) or a new application of an approved product, within 30 days of screening were also excluded from participating in the trials.

Treatment response

The primary outcome measure of this study was to evaluate the mean effectiveness of NEM® in relieving general pain associated with moderate osteoarthritis of the knee and/or hip (Questions 1-9). Additional outcome measures were to evaluate general stiffness (Question 10) and analgesic use during the study. The primary treatment response endpoints were the 10-, 30-, and 60-day patient assessments utilizing a 10-question 'Short Form' questionnaire derived from the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire (WOMAC), which has some precedence [16,17]. Each question included a zero to 10 analog Likert-scale, with zero equating to no pain (or no stiffness) and 10 equating to most severe pain (or most severe stiffness). Patients were asked to mark a number corresponding to the perceived pain (or stiffness) from the affected

treatment joint(s). Endpoints were then compared to pretreatment assessments. At the conclusion of the study, subjects were asked to provide a Patient's Global Assessment of treatment efficacy (4 categories-very good/good/moderate/poor) and tolerability (same 4 categories). Clinical investigators were also asked to provide a Physician's Global Assessment of treatment efficacy (5 categories-symptom-free/significant improvement/moderate improvement/unchanged/impaired).

Adverse events

A secondary objective of this study was to evaluate tolerability and any adverse reactions associated with supplementation with NEM®. The subject's self-assessment diaries were reviewed and any discomfort or other adverse events were recorded and reported in accordance with applicable ICH Guidelines. Adverse events and serious adverse events were assessed by the clinical investigator at each study visit and followed until resolution, as necessary. Serious adverse events were required to be reported to the clinical monitor immediately.

Statistical analysis

As this was an open-label study, a simple single group sample size estimate [18] was performed for statistical power determination for a continuous variable. In previous trials with NEM® [6,7], the standard deviation for the study subjects for pain (within the inclusion range of this study) averaged 34.6%. We hoped to be able to detect a 1.5 point difference from baseline within the 10-point Likert scale. Thus a minimum of 43 subjects would need to be enrolled to have a 95% likelihood of detecting the expected improvement with a statistical power of 80%. Comparisons of demographic data from the six clinical sites were made with a Kruskal-Wallis test for multiple independent samples at baseline. Statistical significance was accepted at $p < 0.05$. Post-baseline statistical analyses were done as repeated measures Analysis of Variance (rm-ANOVA) with a Greenhouse-Geisser correction. Items found to have statistical significance with rm-ANOVA were then compared using a Wilcoxon test for dependent samples. Statistical significance was accepted at $p < 0.05$. Analysis of the primary outcome measure (the change from baseline in general pain levels) was conducted in the per protocol population. SPSS Statistics V19.0 was used for all statistical analyses [19].

Results

Patient recruitment began in March 2012 at six clinical sites in Germany and the final follow-up was conducted in July 2012. A total of forty-four subjects between the ages of 32 and 95 were enrolled with

Age, yrs	67.1 ± 14.0
Sex	
Male (%)	17 (39)
Female (%)	27 (61)
Height, cm	170.2 ± 9.5
Weight, kg	74.2 ± 13.1
Body-mass Index	25.5 ± 4.1
Affected Joint	
Knee (l,r,bilateral)	39 (28,27,16)
Hip (l,r,bilateral)	14 (11,10,7)
Ankle (l,r,bilateral)	3 (2,2,1)

*Except where indicated otherwise, values are reported as mean ± standard deviation (SD) (n=44). BMI was determined as weight in kilograms divided by height in meters squared.

Table 1: Patient Demographics*.

Question 1: Pain when walking on level ground?	4.8 ± 1.0
Question 2: Pain when going up or down stairs?	5.7 ± 1.0
Question 3: Pain when at rest (i.e. sitting, lying down, etc.)?	5.3 ± 1.0
Question 4: Pain when sitting with legs bent for an extended period of time (i.e. in a car, at a theater, etc.)?	3.4 ± 1.8
Question 5: Pain when getting up from a seated position?	5.3 ± 1.3
Question 6: Pain when getting in and out of a car, a bathtub, etc.?	5.3 ± 1.1
Question 7: Pain when bending, stooping, or kneeling?	5.7 ± 1.3
Question 8: Pain when putting on socks or pantyhose?	4.4 ± 1.9
Question 9: Pain with light household chores (i.e. laundry, dusting, vacuuming, etc.)?	4.6 ± 1.7
Question 10: Stiffness when first getting up from bed in the morning?	4.2 ± 1.8

*Values are reported as mean ± standard deviation (SD) (n=37)

Table 2: Pooled baseline clinical characteristics for the 10-question patient questionnaire.

	Days Post-treatment	Mean ± SD	Percent Improvement	P-value†		Days Post-treatment	Mean ± SD	Percent Improvement	P-value†
Question 1	Baseline (n=37)	4.8 ± 1.0	-	-	Question 6	Baseline (n=37)	5.3 ± 1.1	-	-
	10 (n=37)	3.9 ± 1.7	18.1%	0.001*		10 (n=37)	4.4 ± 1.3	15.4%	0.001*
	30 (n=37)	3.3 ± 1.5	30.7%	<0.001*		30 (n=37)	3.7 ± 1.3	29.1%	<0.001*
	60 (n=37)	3.3 ± 1.8	32.4%	<0.001*		60 (n=37)	3.5 ± 1.6	32.8%	<0.001*
Question 2	Baseline (n=37)	5.7 ± 1.0	-	-	Question 7	Baseline (n=37)	5.7 ± 1.3	-	-
	10 (n=37)	4.7 ± 1.7	17.7%	0.001*		10 (n=37)	5.2 ± 1.7	8.6%	0.056
	30 (n=37)	4.1 ± 1.6	26.7%	<0.001*		30 (n=37)	4.4 ± 1.6	22.4%	<0.001*
	60 (n=37)	3.8 ± 1.8	32.6%	<0.001*		60 (n=37)	4.1 ± 1.7	28.0%	<0.001*
Question 3	Baseline (n=37)	5.3 ± 1.0	-	-	Question 8	Baseline (n=37)	4.4 ± 1.9	-	-
	10 (n=37)	4.5 ± 1.5	14.3%	0.001*		10 (n=37)	4.0 ± 1.7	9.2%	0.064
	30 (n=37)	3.8 ± 1.4	27.5%	<0.001*		30 (n=37)	3.2 ± 1.7	25.5%	<0.001*
	60 (n=37)	3.6 ± 1.5	32.6%	<0.001*		60 (n=37)	2.9 ± 1.7	33.6%	<0.001*
Question 4	Baseline (n=37)	3.4 ± 1.8	-	-	Question 9	Baseline (n=37)	4.6 ± 1.7	-	-
	10 (n=37)	2.9 ± 1.9	15.7%	0.042*		10 (n=37)	4.1 ± 1.4	11.7%	0.041*
	30 (n=37)	2.3 ± 1.4	33.8%	<0.001*		30 (n=37)	3.6 ± 1.4	23.0%	0.002*
	60 (n=37)	2.2 ± 2.0	35.6%	<0.001*		60 (n=37)	3.0 ± 1.7	34.9%	<0.001*
Question 5	Baseline (n=37)	5.3 ± 1.3	-	-	Question 10	Baseline (n=37)	4.2 ± 1.8	-	-
	10 (n=37)	4.7 ± 1.6	11.7%	0.012*		10 (n=37)	3.8 ± 1.9	9.9%	0.075
	30 (n=37)	4.0 ± 1.3	24.0%	<0.001*		30 (n=37)	3.0 ± 1.8	27.4%	<0.001*
	60 (n=37)	3.6 ± 2.0	31.7%	<0.001*		60 (n=37)	2.9 ± 1.7	29.3%	<0.001*

†P-values were determined by Wilcoxon test for dependent samples following a statistically significant difference as determined by rm-ANOVA, and represent treatment versus baseline. *P<0.05.

Table 3: Mean values by question in an NEM-supplemented treatment group at baseline and 10, 30 and 60 days post-treatment.

osteoarthritis of the knee and/or hip. Of these subjects, twenty-seven (61%) were female and seventeen (39%) were male. The treated joints consisted of knee (39), hip (14), ankle (3), both either knee and hip (10), or both knee and ankle (2). Of the thirty-nine subjects with knee OA, sixteen (40.0%) had bilateral incidence. Of the fourteen subjects with hip OA, seven (50.0%) had bilateral incidence. Patient demographics are reported in Table 1. All forty-four subjects completed baseline evaluations. Thirty-seven (84%) of the forty-four subjects completed the two month study per the protocol. Compliance with the study treatment regimen was good.

Patient data was initially evaluated between sites to exclude site bias (not shown). As there were no abnormalities in these evaluations, the data were pooled for all subsequent analyses. A clinical comparison of valid subjects was carried out to obtain a mean baseline score for each of the ten questions from the patient questionnaire (Table 2). Statistical analysis of the primary outcome measure revealed that supplementation with NEM® produced a significant treatment response from baseline at 10 days (Q1-6 and Q9) (8.6% to 18.1% improvement) and at 30 and

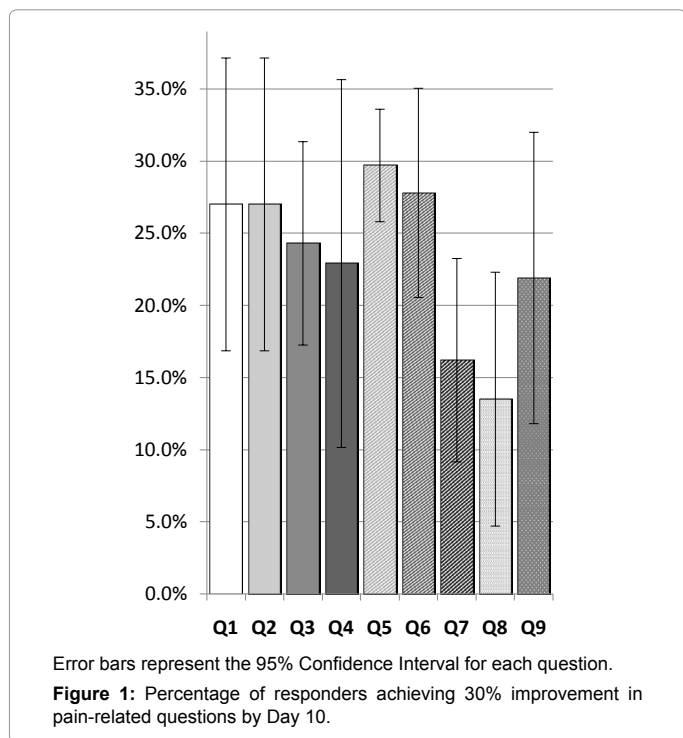
60 days for all nine pain-related questions evaluated (22.4% to 35.6% improvement) (Table 3). Treatment response fell just shy of statistical significance at 10 days for Questions 7 and 8 (p=0.056 and p=0.064, respectively). Supplementation with NEM® produced a significant treatment response from baseline at 30 and 60 days for stiffness (Q10) (27.4% to 29.3% improvement). Greater than 59% of patients rated the efficacy of NEM® as good or very good (Table 4) following 60 days of supplementation. Physicians also rated the treatment effective in subjects, with greater than 75% having moderate or significant improvement from baseline after 60 days (Table 5). For the 30 days prior to study commencement, patients consumed on average 7.0 ± 6.0 doses of acetaminophen. Analgesic use had dropped considerably to 2.43 ± 2.69 doses (per 30 days) at 30 days of supplementation with NEM®. Analgesic use rebounded slightly to 3.59 ± 3.86 doses (per 30 days) by the end of the study at day 60. There were two adverse events reported during the study. One was a scratchy throat and was believed to be related to antibiotic use. The other was stomach discomfort which was believed to be related to the study material. There were no serious

Patient's Global Assessment				
	Efficacy		Tolerability	
	Number	Frequency	Number	Frequency
very good	10	27.0%	22	59.5%
good	12	32.4%	10	27.0%
moderate	9	24.3%	2	5.4%
poor	6	16.2%	3	8.1%

Table 4: Patient's Global Assessment of Efficacy and Tolerability following 60 days of NEM® supplementation.

Physician's Global Assessment		
	Treatment response	
	Number	Frequency
symptom-free	0	0.0%
significant improvement	17	45.9%
moderate improvement	11	29.7%
unchanged	9	24.3%
impaired	0	0.0%

Table 5: Physician's Global Assessment of treatment response following 60 days of NEM® supplementation.



adverse events reported during the study. The treatment was reported to be well tolerated by study participants with greater than 86% of patients rating NEM® tolerability as good or very good

Discussion

Joint and connective tissue disorders are quite common in Westernized countries [1,20] and result in significant costs, both financial [21] and quality-of-life [22], for those that suffer from the debilitating diseases. This open-label clinical trial was designed to evaluate the acceptability of this natural arthritis treatment with European orthopedic surgeons and patients and to validate the

extension of the body of clinical evidence for NEM® from the United States to a European population through the evaluation of the efficacy, safety, and tolerability of NEM® brand eggshell membrane as a treatment option for osteoarthritis of the knee and/or hip. Results of the study indeed suggest that NEM® is both effective and safe for treating pain associated with osteoarthritis of the knee and/or hip in a European population.

Patients experienced relatively rapid (10 days) responses for pain-related questions with a mean response of approximately 14%. By the end of the follow-up period (60 days) the mean response for pain-related questions had more than doubled to approximately 33%. A brief responder analysis of the data provides a number of clinically relevant highlights. On average, nearly 1/4th of the subjects experienced a 30% improvement in pain-related questions within 10 days (Figure 1). And almost 20% of the study population experienced a 50% improvement in pain-related questions by the end of the study (60 days) (not shown). These results align well with results from previous clinical studies of NEM® that were conducted in the U.S. [6,7].

The safety profile for NEM® is also of significance as this is the fifth clinical trial to date in which there have been no reports of serious adverse events associated with treatment. No side effects from consuming NEM® have thus far been identified, excluding the obvious egg allergy concern. This is of obvious importance in a condition such as osteoarthritis that requires long-term treatment.

The trial had a limited initial enrollment (44 subjects), however there was a relatively low drop-out rate (16%) and good treatment compliance. As the trial was also open label, there is the obvious issue of the placebo effect. The inclusion of a placebo control would have provided greater clinical meaning, however it would have required a significantly larger study population.

Conclusions

With so many people suffering from osteoarthritis of the knee and hip in Western populations, it is important for patients to have treatment options that are both safe and effective. The reporting of the results from this six center, open label German clinical study demonstrates that NEM® brand eggshell membrane may be a viable treatment option for the management of osteoarthritis of the knee and/or hip in the broader European population. In this clinical study, NEM®, 500 mg taken once daily, significantly reduced pain, both rapidly (10 days) and continuously (60 days). It also showed clinically meaningful results from a brief responder analysis, demonstrating that a significant proportion of treated patients will benefit from NEM® supplementation.

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