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POS-278 PULSED SIGNAL THERAPY FOR THE TREATMENT OF OSTEOARTHRITIS: DOUBLE BLIND AND RANDOMIZED STUDY RESULTS IN OVER 50,000 PATIENTS

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Double-blind clinical trials and other open label randomized studies were conducted in the USA, Canada, France, Italy and Germany, to determine the effectiveness of a specific pulsed electromagnetic field called Pulsed Signal Therapy [pulsed DC magnetic field: 0.28 W., max. 20 gauss; 5–24 Hz; quasi-rectangular wave form], for the treatment of osteoarthritis of the knee, hip, lower back and cervical spine. Previous studies had shown that changes in placebo groups had less significance at the end of treatment, and had lost significance for most variables at the one-month follow-up. In contrast, treatment groups consistently demonstrated statistically significant and sustained benefits.

Controlled double-blind and observational open label studies were undertaken by Dr. David H. Trock and Alfred J. Bollet at Danbury Hospital, Conn. USA, (Teaching Affiliate of Yale University School of Medicine), Dr. Cecil Hershler, University of Vancouver, Canada, Prof. Menkes, Cochin Hospital, Paris, France, Prof. Radaelli, Ospedale Niguarda – Ca Granda, Milan, Italy, Prof. Fhr. von Gumppenberg, TU University School of Medicine OM, Munich, Germany and Prof. Rainer Breul, LMU University School of Medicine, Munich Germany. More than 50,000 patients have been studied worldwide to date.

Initially, 18 half-hour treatments and then 9 one-hour treatments, (active or placebo in the double-blind and active in the open label studies) were conducted over a ten year period in the USA, Canada and Europe. Pain was evaluated using WOMAC and later OMERACT III validated instruments of outcome measures. Functionality was measured using WOMAC and modified Ritchie scales, as well as global evaluations of improvement by the patient and examining physician. The LMU two year multi-center clinical study completed November 1999 produced data from >20,000 patients treated in 104 PST clinics throughout Germany. Data from the LMU multi-center study will be collected until the end of 2002.

Matched pair tests and other statistical analysis showed highly significant changes from baseline for the treated patients irrespective of the joint treated. The changes in the placebo patients showed lesser degrees of significance at the end of treatment, and had lost significance for most variables at the one month follow up. The open label analysis and results were consistent with the double-blind results.

Pulsed Signal Therapy (PST) provides significant improvement in pain and limitation of motion, the two major complaints of patients suffering from osteoarthritis. It is not associated with any discomfort or side effects, and long-term follow-up evaluation has confirmed its safety, sustained improvement, and cost effectiveness. PST is a patented, non-invasive treatment that should not be confused with other approaches or devices frequently described or referred to as Pulsed Electromagnetic Field Therapy; the most important difference lies in the variability of the amplitude and repetition rate that is employed in PST.

POS-279 MK-0663: A HIGHLY SELECTIVE INHIBITOR OF COX-2 IN HUMANS

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MK-0663 is a potent and specific inhibitor of COX-2 with an *in vitro* IC_{50} of 1.09 μM in an LPS-stimulated whole blood PGE_2 assay (LPS-PGE_2) for COX-2, and 116 μM in a serum TXB_2 assay for COX-1. The relative *in vitro* IC_{50}s for COX-1 and COX-2 demonstrate a higher selectivity for MK-0663 compared to other NSAIDs and COXIBs. *Ex vivo* assays were used to demonstrate selective COX-2 inhibitory activity after oral administration of MK-0663 to healthy subjects (n = 6 active, n = 2 placebo in each panel). In a single dose study, subjects were dosed with MK-0663 (5 to 500 mg) or placebo. In a multiple dose study, subjects were dosed with MK-0663 (25, 50, 100 or 150 mg) or placebo once daily for 9 days. Plasma samples were obtained to measure drug levels.

After single doses of 5 to 500 mg, mean C_{max} ranged from 0.2 to 21.8 μM. After multiple doses (steady state), mean C_{max} ranged from 1.5 to 8.2 μM for 25 to 150 mg dose groups. The maximum mean inhibition of LPS-PGE_2 (I_{max}) was 12.6, 20.3, 37.0, 39.5, 71.6, 85.4, 94.6 and 92.1% after single doses of placebo, 5, 10, 25, 50, 125, 250, and 500 mg MK-0663, respectively. On day 9 of multiple dosing, I_{max} was 13.1, 75.3, 62.1, 81.6 and 93.3% for placebo, 25, 50, 100 and 150 mg groups, respectively. PGE_2 remained significantly inhibited 24 hours postdose at steady state. Inhibition of LPS-PGE_2 correlated with MK-0663 plasma levels. The *ex vivo* IC_{50} was ~1 μM, similar to the *in vitro* result. There was no significant effect on serum TXB_2 with multiple dosing of MK-0663 150 mg once daily, consistent with *in vitro* results. MK-0663 was well tolerated, and, at steady state, had no effect on bleeding time or platelet aggregation induced by arachidonic acid (COX-1 mediated effects).

The results demonstrate that MK-0663 is a potent and specific inhibitor of COX-2 after single and multiple dosing regimens.

POS-280 MODULATION OF sTNF-R55 AND sTNF-R75 BY MUD PACK TREATMENT IN OSTEOARTHROSIS

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Objective: to investigate the influence of mud pack therapy (MPT) on serum TNF receptors (sTNF-Rs) values.

Several growth factors and cytokines have an important and well established role in the pathophysiology of inflammatory joint diseases (Feldmann M et al, 1991, Farahat MN 1993), particularly TNFα plays a pivotal role in the cartilage degenerative process, and its biological activity is modulating by binding specific TNF receptors on cells surface (Aggarwal BB et al 1996; Porteu F et al 1994). Recent data show that there are soluble TNF receptors (sTNF-Rs) circulating, which can bind and inactivate TNF.

In our study we investigated the influence of mud pack treatment, which is able to diminish TNFα serum levels (Bellometti et al, 1997) on sTNF-Rs values.

We enrolled 36 osteoarthrosic patients, randomized in two groups underwent MPT (groupA) and thermal bath treatment (group B). We collected blood samples at baseline and after the treatment to assay sTNF-R55 and sTNF-R75 serum levels by sandwich enzyme-immunoassay, using monoclonal antibodies.

The study shows little variations in sTNF-Rs serum values, with no statistically significant differences between the two receptors type

	sTNF-R55 (pg/ml)			sTNF-R75 (pg/ml)		
	before	after	Δ%	before	after	Δ%
Group A	1262 ± 590	1267 ± 423	−0.4	4373 ± 1953	3447 ± 1244	−21.7
Group B	1324 ± 504	1089 ± 381	−17.7%	4680 ± 1612	4183 ± 768	−10.6

MPT exerts a very complex interaction with the more common factors of inflammatory and cartilage degradation processes. This natural treatment partecipates in modulation of inflammatory reaction and cartilage damage by favouting the bind of circulating TNFα to its natural inhibitors.

POS-281 SYNOVIAL THICKENING IN OSTEOARTHRITIS: A DISTINCT CLINICAL SUBSET?

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Background: synovial effusion, sometimes with accompanying mild synovitis, can be a feature of osteoarthritis (OA). Synovial thickening (ST) can be found on ultrasound (US) examination in some patients with OA.

Objectives: to assess the clinical characteristics of patients with knee OA and ST as detected by US and to evaluate whether these patients show any distinctive features compared with patients with knee OA with effusion but lacking ST.

Methods: 32 (27 F/5 M, mean age 68 ± 9 y) consecutive patients presenting with use-related knee pain and radiographic features of OA and with signs of synovial effusion and without any clinical or laboratory evidence of inflammatory arthropathy. Age, sex, body mass index (BMI), presence of OA at other sites, duration of symptoms, knee pain (10-cm VAS), radiographic severity (Kellgren score), bone scintigraphy abnormalities, US findings and the Lequesne index were analysed.

Results: 3 out of the 32 selected patients did not show evidence of synovial effussion on US examination and were not analysed. 7/29 (24%) had ST detected by ultrosound; all of them were women. The ST was distributed focally, especially in the internal and suprapatellar compartments, with a mean thickening of 4.5 ± 2.7 mm (3.2–7.9 mm). Those with a more prominent thickening tended to have more pain and higher Lequesne index scores. Compared with the patients from the group with only synovial effusion, those with ST had more pain on use and at rest by VAS (5.6 vs 3.8, $p = 0.04$), a higher Lequesne index (9.6 vs 4.2, $p < 0.01$) and a tendency toward a lower BMI (24.3 vs 31.5, $p = 0.065$). Interphalangeal and carpometaacarpal joint of hand involvement were also more frequent in the ST group (4/7 (57.1%) vs 10/22 (45.4%) and 5/7 (71.4%) vs 12/22 (54.5%), respectively. There were no differences in age, disease duration, radiographic severity. There were no differences in the synovial fluid aspirated, which always was noninflammatory. Interestingly, 6/7 (85.7%) patients with ST demonstrated by US had a scintigraphic pattern of generalised isotope uptake (vs 7/22 (31%) in the control group, $p < 0.01$) and 3/7 (42.8%) in the late phase, which could reflect an inflammatory process, whereas among the patients without synovial thickening was more frequent "tramline" scintigraphic pattern. The patients with ST appeared to have a poorer response to paracetamol and had a greater use of NSAIDs. An history of intra-articular steroid injection was also more frequent in the ST group and in general had proved to be effective.

Conclusions: Knee OA with synovial thickening on US examination appear to have some distinctive features, having a more severe clinical disease. Further study is needed to confirm these data and better define this subset of patients, especially the potential prognostic and management implications.