SAFETY AND EFFICACY OF INTRAMUSCULAR SODIUM RIBONUCLEINATE [OSTEOCHONDRIN S] FOR RELIEF OF PAIN AND JOINT FUNCTIONS IN KNEE OSTEOARTHRITIS

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Introduction

Osteochondrin S [OST] is a natural ribonucleotide extract of bovine-derived connective tissues (from accredited BSE-free sources) and yeast which has been found to reduce joint damage in some animal models of joint injury (Rainsford, 1996) and inhibits cytokine-induced cartilage-bone degradation *in vitro* (Rainsford et al., 2008). Symptom trials have been performed showing that this drug is effective in controlling indices (WOMAC) of joint pain and physical function in osteoarthritis [OA] (Rainsford, 1996; Rainsford et al., 2004). However, a comprehensive clinical evaluation of the safety in relationship to the effectiveness of this preparation in patients with OA has not been performed previously. Hence, in the present study, we undertook a randomised, placebo-controlled, parallel-group study in 166 patients (of whom 145 were evaluable) with OA of the knee at 20 centres in Germany performed under ICH-GCP conditions, the design of this study and part of the efficacy determinations have been reported previously (Rainsford et al., 2004). We also report results of observations on the safety of OST from investigations from a related study in Moscow and previous clinical trials and spontaneous reports.

Materials and Methods

Study Objectives

- Determination of the efficacy of OST compared with PLA in three treatment series by means of components of the WOMAC-Index and the relief of pain assessed by the intake of Ibuprofen as a rescue medication.

Study Design

- Prospective, randomised, double-blind, parallel, placebo controlled phase III multi-centre trial in patients with radiologically-established symptomatic osteoarthritis of the knee (gonarthritis)

Number of patients

- Study population (= safety population) of the 3-series-trial: N=166 patients in a two arm treatment (OST N=84; PLA N=82)

- Two trial centres were excluded from efficacy analysis due to major non-compliance with the study conditions

- Full analysis set (FAS): 145 patients (OST: N=72; PLA: N=73)
  Valid case set (VC): 120 patients (OST: N=60; PLA: N=60)

Main criteria for inclusion

- Pain in the knees for at least half of the day in the preceding 2 months before the trial

- aged between 40 and 75 years

- WOMAC Indices for PAIN ≥ 200 and for JOINT STIFFNESS ≥ 80 (for details about WOMAC Indices see Figure 1)

Western Ontario und McMaster University Osteoarthritis (WOMAC) Index

The WOMAC-Index describes the severity of the osteoarthritis by 24 **V**isual **A**nalog **S**cales (VAS with range 0-100) in three dimensions:

- pain-dimension
  values of 5 criteria are added to the dimension pain (range 0-500):
  pain during walking, pain during stair climbing, nocturnal pain, pain at rest, weight bearing pain

- dimension joint stiffness
  values of 2 criteria are added to the dimension joint stiffness (range 0-200):
  morning stiffness, stiffness occurring later in the day

- dimension physical function
  values of 17 criteria are added to the dimension physical function (range 0-1700):
  descending stairs, ascending stairs, rising from sitting, standing, bending to floor, walking on flat, getting in/out car, going shopping, putting on socks, rising from bed, taking of socks, lying in bed, getting in/out bath, sitting, getting on/off toilet, heavy domestic duties, light domestic duties.

Figure 1: WOMAC Index

Test product

- Osteochondrin S ampoules à 5 mL. One ampoule contains 6,3 mg sodium ribonucleinate (from bovine intervertebral disc, synovia, cartilage, placenta and from yeast)

Dosage and mode of administration

- 3 x 2 ampoules i.m. injections per week in 20 ampoules series

Main criteria for efficacy and safety evaluation

- Primary endpoint:
  Responder rates of the WOMAC total index in the average of series 2 and 3 in the FAS / VC set.
  (Response = reduction ≥ 20 % as compared with baseline)

- Adverse events

- Laboratory findings

- Physical examination and vital signs

- Global assessment of tolerability

Statistical assessment

- U test, t-test, X^2 test (one sided tests)
- Logistic regression (two sided tests of odds ratios)
- Significance level α=0,025 one-sided and α= 0,05 two-sided

Treatment schedules

The flow diagram in Figure 2 shows the overall organisation of the treatment schedule

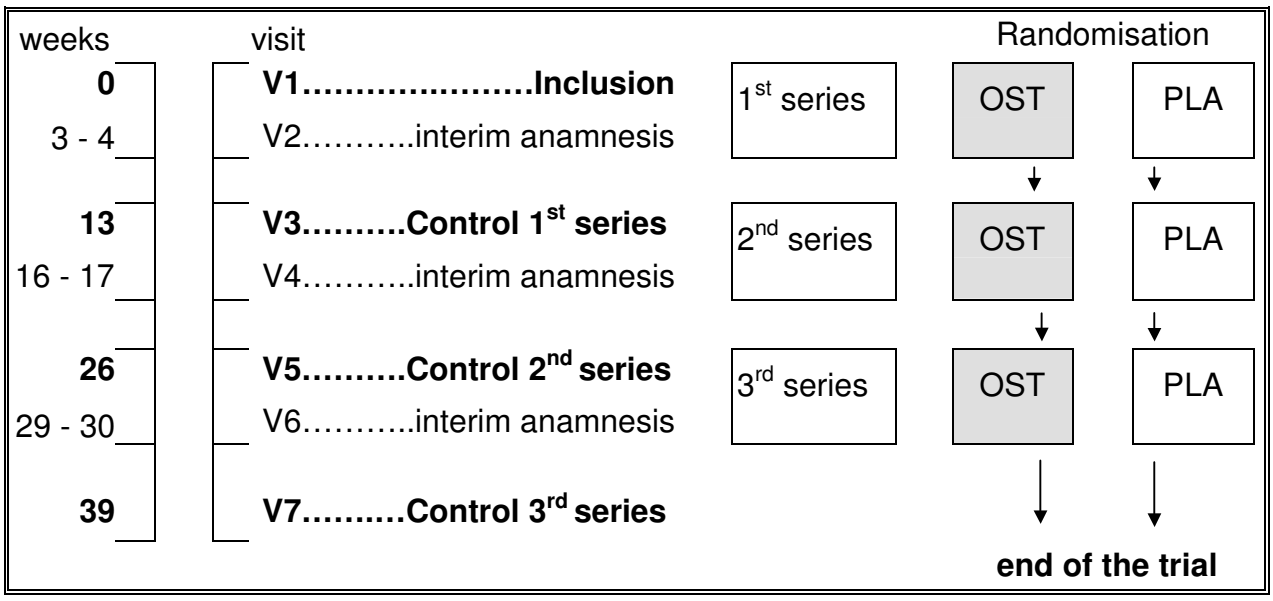

Figure 2: Treatment and observation assessment

Results

Drug Safety

Adverse events (AEs)

- The study was terminated prematurely due to adverse events in 4 OST and 3 PLA patients.

- In total, adverse events were observed in 101 patients as shown in Table 1

Number of patients [N] with observed adverse events	
Osteochondrin S: N = 48 cases (57,1%)	Placebo: N = 53 cases (64,6%)
No statistically significant differences between the trial groups (X^2 test: p=0,323)	

Table 1: Number of adverse events in both trial groups

- Adverse events have been classified according to WHO terms of "System Organ Classes" (SOCs). The most frequent events have been found in 4 SOCs:

  body as a whole – general disorders

  gastro-intestinal system disorders

  musculo-skeletal system disorders and respiratory system disorders

The incidences of adverse events on the basis of SOCs is shown in Table 2

SOC	OST [N=84]		PLA [N=82]		X^2 test
	N	%	N	%	(p-value)
Skin and appendages disorders	9	10,7	6	7,3	0,445
Musculo-skeletal system disorders	9	10,7	15	18,3	0,165
Central & peripheral nervous system disord.	5	6,0	7	8,5	0,520
Vision disorders	2	2,4	2	2,4	0,981
Hearing and vestibular disorders	2	2,4	1	1,2	0,574
Psychiatric disorders	5	6,0	5	6,1	0,969
Gastro-intestinal system disorders	11	13,1	17	20,7	0,189
Liver and biliary system disorders	1	1,2	1	1,2	0,986
Metabolic and nutritional disorders	4	4,8	2	2,4	0,423
Endocrine disorders	-		1	1,2	0,310
Cardiovascular disorders, general	4	4,8	7	8,5	0,328
Myo-, endo-, pericardial & valve disorders	1	1,2	2	2,4	0,560
Heart rate and rhythm disorders	-		1	1,2	0,310
Vascular (extracardiac) disorders	3	3,6	2	2,	0,670
Respiratory system disorders	7	8,3	12	1,6	0,202
Red blood cell disorders	-		1	1,2	0,310
White cell and reticuloendothelial system disorders	1	1,2	-		0,322
Platelet, bleeding & clotting disorders	2	2,4	-		0,160
Urinary system disorders	4	4,8	3	3,7	0,724
Reproductive disorders, male	1	1,2	-		0,322
Reproductive disorders, female	-		2	2,4	0,150
Neoplasm	-		1	1,2	0,310
Body as a whole – general disorders	20	23,8	19	23,2	0,923
Resistance mechanism disorders	6	7,1	7	8,5	0,738
Operations	-		1	1,2	0,310
Injuries	4	4,8	8	9,8	0,214

Table 2: Frequency of adverse event related symptoms classified according to WHO System Organ Classes (SOCs). NO significant group differences (level α=0,150) could be detected

Drug related adverse events

- The relationship to the study drug was assumed to be related to treatment
  in 5 (6 %) cases (OST) and 6 (7,3%) cases (PLA) corresponding to symptoms shown in Table 3

OST	
WHO preferred terms	**Action**
Pruritus	no action taken
Circulatory failure	study drug discontinued
Rash erythematous	study drug discontinued
Sweating increased; Cramps legs	no action taken
Headache	no action taken
PLA	
WHO preferred term	**Action**
Myalgia	check for thrombosis
Arthralgia	study drug discontinued
Paraesthesia	no action taken
Arthralgia; Hypoaesthesia; Fatigue and pain	no action taken
Dizziness; Fatigue	no action taken
Somnolence	study drug discontinued

Table 3: Symptoms listed as WHO preferred terms from cases related to the study drug

- The SOC “Skin and appendages disorders” was frequented 3 times in the verum group only (X^2 test: p = 0,084), the SOC “Musculo-skeletal system disorders” was 3 times in the placebo group only (X^2 test: p = 0,077)

Serious adverse events

- 4 cases of serious adverse events occurred in both treatment groups each. The relationship with the study drug was excluded or rated unlikely. There were no deaths or serious sequelae.

Laboratory parameters

Changes from baseline to endpoint in each individual laboratory parameter were compared between the trial groups as shown in Table 4

Parameter		OST			PLA			t-test (p-value)
		N	X	SD	N	X	SD	
Leucocytes	[10^9/L]	74	0,32	2,36	75	-0,02	1,76	0,332
Erythrocytes	[10^{12}/L]	74	0,01	0,40	75	-0,02	0,34	0,617
Haematocrit	[%]	74	-0,05	3,14	75	0,22	2,33	0,546
Haemoglobin	[g/dL]	74	-0,08	1,04	75	0,07	0,82	0,351
Platelets	[10^9/L]	74	-8,62	58,27	76	1,91	69,20	0,316
Neutrophils	[%]	70	-0,10	8,51	70	0,59	8,17	0,622
Basophils	[%]	70	0,16	1,31	70	-0,07	0,78	0,214
Eosinophils	[%]	70	-0,25	1,70	70	-0,00	2,55	0,503
Lymphocytes	[%]	70	0,11	7,14	70	-0,30	6,85	0,731
Monocytes	[%]	70	-0,14	3,07	70	-0,07	2,07	0,882
Others	[%]	70	0,19	1,27	70	-0,17	1,72	0,161
Quick's time	[%]	68	0,81	7,26	67	-0,81	6,95	0,190
PTT	[sec]	61	-0,23	3,25	61	-0,54	5,23	0,698
Sodium	[mmol/L]	70	1,51	4,46	76	0,84	4,13	0,346
Potassium	[mmol/L]	71	-0,16	0,87	76	-0,20	0,67	0,762
Calcium	[mmol/L]	71	-0,03	0,15	73	0.01	0,30	0,314
Phosphate	[mg/L]	44	-0,11	0,98	45	-0,04	1,11	0,736
Glucose	[mg/dL]	72	-5,51	40,05	75	0,89	20,52	0,222
Total cholesterol	[mg/dL]	74	-5,91	36,03	75	-12,43	28,98	0,225
LDL cholesterol	[mg/dL]	55	-9,38	29,74	56	-7,50	20,56	0,699
HDL cholesterol	[mg/dL]	54	-0,62	10,39	54	3,40	12,19	0,068
Triglycerides	[mg/dL]	72	9,19	62,82	74	-7,47	53,21	0,086
Creatinine	[mg/dL]	74	0,00	0,14	76	0,00	0,10	0,986
Uric acid	[mg/dL]	73	-0,02	1,23	76	0,04	1,01	0,723
Urea	[mg/dL]	58	2,05	8,50	63	0,32	9,89	0,308
Blood-urea nitrogen	[mg/dL]	6	0,60	5,50	5	4,80	8,29	0,340
GOT (AST)	[U/L]	74	-0,10	3,22	72	0,85	5,29	0,193
GPT (ALT)	[U/L]	72	1,13	4,70	76	0,24	7,62	0,398
γ-GT	[U/L]	74	0,65	12,04	76	4,92	35,16	0,323
Alk. phosphatase	[U/L]	71	1,51	30,01	74	7,12	59,02	0,474
Total bilirubin	[mg/dL]	68	-0,04	0,19	69	0,03	0,20	0,036

Table 4: Laboratory findings from clinical chemistry and haematological screening.

Statistically significant difference of the p-value < 0,150 was obtained in 3 variables:

HDL cholesterol (p = 0,068):
OST: decrease by 0,6 ± 10,4 from 56,2 ± 20,2 to 55,6 ± 18,4 mg/dL
PLA: increase by 3,4 ± 12,2 from 51,4 ± 11,8 to 54,8 ± 16,7 mg/dL
Differences were due to different baseline values (clinically not significant)

Triglycerides (p = 0,086)
OST: increase by 9,2 ± 62,8 from 143,3 ± 70,5 to 152,4 ± 79,5 mg/dL
PLA: decrease by 7,5 ± 53,2 from 158,2 ± 99,2 to 150,8 ± 103,5 mg/dL
Differences were due to different baseline values (clinically not significant)

Total bilirubin (p = 0,036)
OST: decrease by 0,04 ± 0,19 from 0,67 ± 0,25 to 0,63 ± 0,25 mg/dL
PLA: increase by 0,03 ± 0,20 from 0,63 ± 0,25 to 0,67 ± 0,28 mg/dL
(clinically not significant changes within normal range)

- Clinically relevant shifts occurred in 2 OST-treated patients (LDL, HDL and total cholesterol resp. triglycerides) and in 1 PLA-treated patient (γ-GT and alk. phosphatase)

Vital signs

- Heart rate and blood pressure were monitored at the begin of the study and at the end. In both treatment groups no relevant changes from baseline were seen in the course of the study.

Global assessment of tolerability

- The global assessment of tolerability at the end of the study is shown for the patient's assessment (Table 5a) and the investigator's assessment (Table 5b)

Patients assessment (p=0,674)				
Judgement	OST		PLA	
	Frequency		Frequency	
very good	50	63,3 %	52	65,0 %
good	28	35,4 %	25	31,3 %
moderate	1	1,3 %	2	2,5 %
bad	-		1	1,3 %

Table 5a: Patients assessment of tolerability

Investigators assessment (p=0,571)				
Judgement	OST		PLA	
	Frequency		Frequency	
very good	52	65,8 %	56	70,0 %
good	26	32,9 %	21	26,3 %
moderate	1	1,3 %	2	2,5 %
bad	-		1	1,3 %

Table 5b: Investigators assessment of tolerability

- At study end the tolerability was rated “good“ or “very good” in nearly all patients:

Other safety observations

- Clinical trial in Moscow
  Additional investigations were performed in 48 patients with Osteoarthritis of the knee under the auspices of Prof. Dr. R.M. Balabanova at the Institute of Rheumatology, Moscow. The protocol used was similar to that in the German multi-centre study. In the safety evaluation there were no recorded cases of serious or non-serious reactions with OST and only one non-serious case with PLA (dry mouth)

Safety data from post-marketing experience

- OST and related products (i.e. natural ribonucleotide extracts from other bovine tissue than used in OST) have been used clinically for decades. Adverse events from spontaneous reports and from clinical trials have been documented. In 35 years before the initiation of the described studies in Germany and Moscow 25 cases of adverse reactions have been reported from the use of OST or related products. The frequency of symptoms classified into SOCs are listed in Table 6.

SOC	**Frequency**	
	Spontaneous report	Clinical trial
Application site disorders	9	11
Skin and appendages disorders	13	1
Body as a whole – general disorders	4	
Psychiatric disorders	1	2
Gastro-intestinal system disorders	1	2
Hearing and vestibular disorders	3	
Cardiovascular disorders, general	3	
Vascular (extracardiac) disorders		2
Respiratory system disorders	2	
Platelet, bleeding & clotting disorders	2	
White cell and reticuloendothelial system disorders	1	
Central & peripheral nervous system disorders	1	

Table 6: Frequency of adverse events from spontaneous reports or clinical trials in the post-marketing period from 1965 – 2000. Symptoms were classified according to WHO SOCs.

- The reported cases were not serious and recovered without intervention.

Efficacy results

- The data obtained in ITT analysis of valid cases showed statistically-significant reduction in pain scores, physical function scores and WOMAC index scores respective the responder rates. The response rates derived from FAS results are shown in Table 7

Variable (WOMAC)	OST	PLA	X^2-test	Regression
Total index	81,9 %	64,4 %	p = 0,0086	p = 0,0063
Pain scale	81,9 %	68,5 %	p = 0,0304	p = 0,0204
Stiffness scale	87,5 %	71,2 %	p = 0,0078	p = 0,0037
Physical function scale	77,8 %	64,4 %	p = 0,0377	p = 0,0403

Table 7: Responder rates of WOMAC index scales

- The superiority of OST was established for the 4 scales simultaneously.

Conclusion

OST has a safety profile that is comparable with that of PLA. The incidence and severity of AEs from treatment with OST in clinical trials and from spontaneous reports over a period of 35 years of clinical use is low and notably less than that seen in many trials with NSAIDs or disease-modifying agents used in OA (e.g. glucosamine, hyaluronic acid).
OST showed superior efficacy over PLA but because of high placebo reactor rates this was more pronounced when the evaluation was performed using responder criteria.

Key References

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