REPORT

Study title

ASSESSMENT OF STABILIZED ORTHOSILICIC ACID ON BONE TURNOVER IN PATIENTS WITH OSTEOPENIA:
ADVERSE EVENTS

Protocol nr. 00/1

Study period

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Confidential
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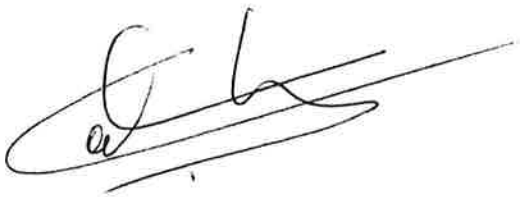

Date: May 18, 2005

2 Introduction

A placebo-controlled study was conducted in 184 women (mean age ± SD: 61 ± 10.4) with documented osteopenia (DEXA of the hip: T-score ≤ -1.5) at the St Thomas' Hospital, London, UK. All patients received daily 1000 mg calcium (calcium carbonate) and 800 IU cholecalciferol (20 μg vit. D3). The study population was randomized in 4 groups. Choline-stabilized orthosilicic acid (ch-OSA) was administered in three groups (table 1) which in this population would increase the dietary Si intake by 12.5, 25 and 50 % respectively. In the placebo group, patients were administered a liquid containing 47 % choline chloride with a similar matrix as ch-OSA.

Table 1: Randomized patient groups.

Group	Supplement, daily dose
1	Placebo, 0 mg Si
2	ch-OSA, 3 mg Si
3	ch-OSA, 6 mg Si
4	ch-OSA, 12 mg Si

3 Biochemical safety parameters

Several biochemical parameters were analyzed in serum (26 items, table 2) and urine parameters (17 items, table 3) at baseline and after 12 months treatment (T12). A significant increase was found after 12 months ch-OSA supplementation (3 mg Si/day) within the normal range for serum sodium concentration. Women who were supplemented with 6 mg Si as ch-OSA showed a significant increase within the normal range for respectively the cupper and magnesium concentration in serum. The daily vitamin D3 supplementation was reflected in a significant increase within the normal range for serum 25-OH-vit. D_3 in all groups.

Baseline values of total cholesterol and LDL-cholesterol were higher than the upper limit of the normal range in both the placebo and the ch-OSA groups (table 2). The mean serum amylase concentration was outside the normal range in the ch-OSA group receiving 3 mg Si both at baseline and after 12 months treatment.

The remaining serum parameters were found within the normal range at baseline and after 12 months treatment in all groups.

No significant differences were found between groups for urine parameters (table 3).

4 Adverse events

Respectively the number of included patients, drop-outs, and patients who completed the 12 months study period, are summarized in figure 1.
Reasons to withdrawn from the study were classified as medical and non-medical (see table 4). Table 5 summarizes patients who dropped out for medical reasons. Four cases were classified as serious adverse events: neuro-endocrine tumor combined with liver cancer, liver cancer combined with gal bladder problems, breast cancer, and cerebro-vascular accident. In 3 of the four cases a disturbed liver function was observed at baseline (table 5). These adverse events were not regarded as related to ch-OSA considering the nature of these pathologies and the disturbed liver function which was observed for these patients at baseline (table 5).

5 Conclusion

Oral intake of ch-OSA in a dose up to 12 mg Si daily during 12 months was regarded as safe as (a) no ch-OSA related adverse events were observed and (b) no clinically relevant changes in biochemical safety parameters were observed.

Fig.1: Flowchart of osteopenia patients supplemented during 12 months with placebo and ch-OSA.

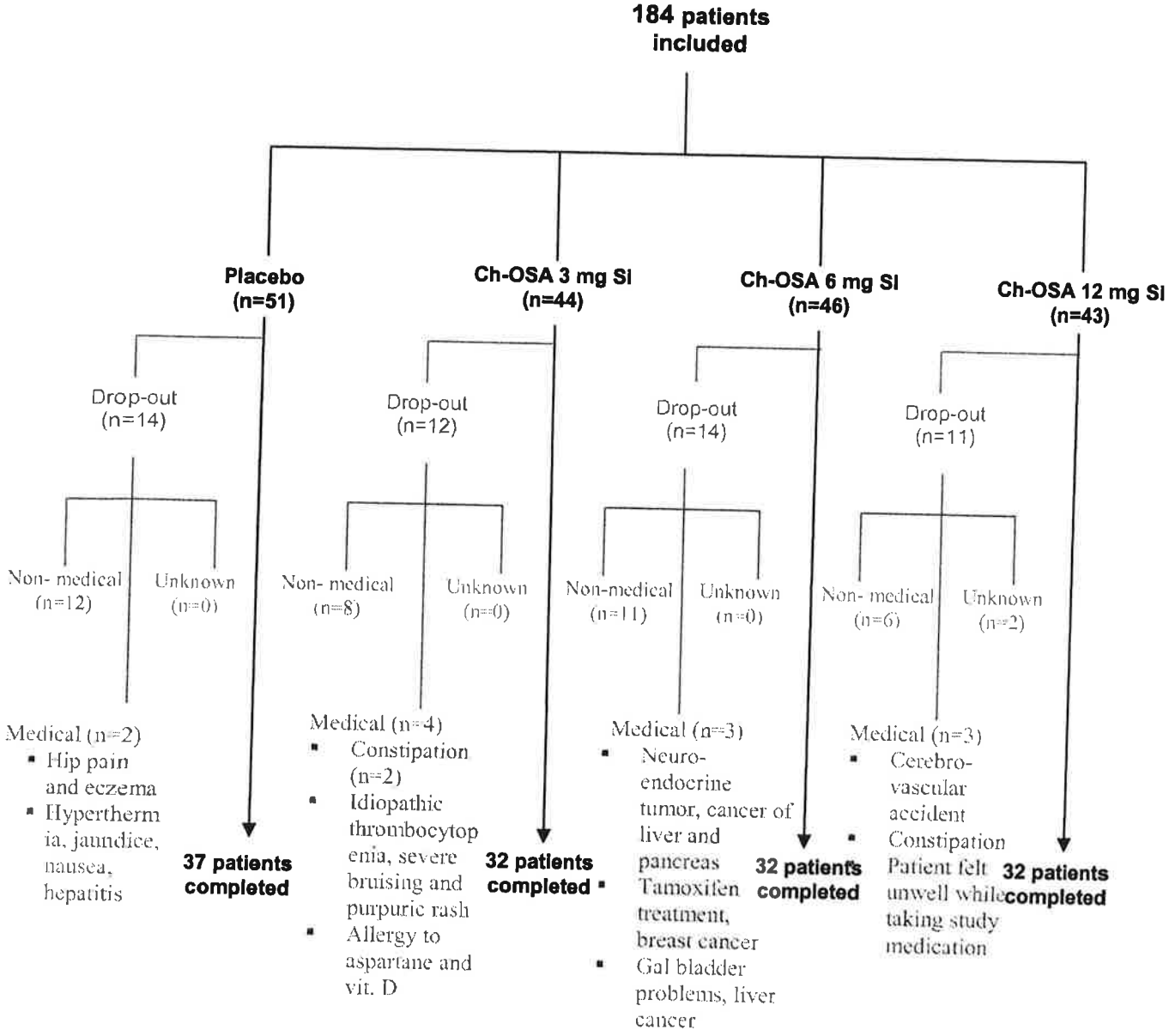

Table 2: Serology parameters in women at baseline and after 12 months.

	Normal range		Placebo; n=37		Ch-OSA (3 mg Si);n=32		Ch-OSA (6 mg Si); n=32		Ch-OSA (12 mg Si); n=32	
	LL	UL	Baseline	T12	Baseline	T12	Baseline	T12	Baseline	T12
Serology										
Glucose (mg/dL)	70	110	87,43 ± 8,41	87,27 ± 6,74	89,03 ± 14,39	88,00 ± 10,32	86,50 ± 8,08	84,38 ± 9,23	86,16 ± 10,16	86,69 ± 9,72
Urea (mg/dL)		50,1	32,27 ± 8,66	32,39 ± 8,60	30,05 ± 8,51	32,46 ± 7,40	28,07 ± 7,45[7]	30,33 ± 8,17[4]	31,71 ± 7,12[2]	30,54 ± 5,93
Creatinine (mg/dL)	0,60	1,40	0,79 ± 0,13	0,83 ± 0,11[4]	0,76 ± 0,14	0,84 ± 0,13[3]	0,72 ± 0,12[7]	0,79 ± 0,11[3]	0,80 ± 0,12[2]	0,82 ± 0,09
Uric acid (mg/dL)	2,6	7,2	5,53 ± 1,07	5,52 ± 1,00	5,92 ± 1,38	6,23 ± 1,51	5,25 ± 1,07	5,09 ± 1,05[1]	5,88 ± 1,01	5,71 ± 0,99
Ferritin (µg/L)	11	250	60,24 ± 38,75	52,38 ± 33,81[3]	63,84 ± 37,24	59,72 ± 36,12	44,97 ± 26,98[7X8]	43,97 ± 32,96[1]	77,09 ± 57,98[2]	66,47 ± 49,59[3X9]
Total proteins (g/dL)	6,4	8,3	7,14 ± 0,51	7,08 ± 0,37	7,00 ± 0,67	7,15 ± 0,32	7,20 ± 0,44	7,00 ± 0,32[3X1]	7,21 ± 0,36	7,13 ± 0,49
Cholesterol (mg/dL)		190	241,59 ± 52,41	236,03 ± 52,09	223,22 ± 49,28	226,53 ± 34,47	241,47 ± 35,61[8]	224,69 ± 26,44[3]	238,25 ± 35,48	226,69 ± 33,52[4]
Triglycerides (mg/dL)		180	105,49 ± 41,12	107,89 ± 51,95	130,28 ± 140,94	108,63 ± 61,67	100,59 ± 41,99	100,38 ± 40,21	101,81 ± 52,76	116,19 ± 110,20
HDL-cholesterol (mg/dL)	40		50,11 ± 12,59	54,86 ± 12,58[3]	48,84 ± 18,54	55,28 ± 15,43[3]	53,13 ± 15,57	54,59 ± 12,94	47,53 ± 14,14	52,69 ± 14,58[3]
LDL-cholesterol (mg/dL)		115	169,95 ± 47,83	159,11 ± 46,14[4]	152,87 ± 45,41	150,90 ± 35,71	167,88 ± 31,09	149,69 ± 24,62[3]	169,61 ± 31,09	152,74 ± 34,18[3]
HDL/LDL			0,32 ± 0,12	0,38 ± 0,15[3]	0,36 ± 0,17	0,40 ± 0,18[3]	0,33 ± 0,12	0,38 ± 0,12[3]	0,30 ± 0,10	0,37 ± 0,13[3]
Bilirubin total (mg/dL)	0,1	1,3	0,43 ± 0,17	0,43 ± 0,17	0,39 ± 0,17	0,40 ± 0,16	0,43 ± 0,18	0,38 ± 0,11[4]	0,46 ± 0,23	0,51± 0,33[6]
SGOT (AST) (U/L)		37	11,27 ± 3,44	13,11 ± 3,03[3]	11,59 ± 4,15	13,44 ± 4,41[3]	10,88 ± 2,88	12,34 ± 3,46[3]	11,28 ± 3,99	12,72 ± 3,74[3]
SGPT (ALT) (U/L)		38	9,57 ± 4,38	8,00 ± 4,01[3]	9,91 ± 5,29	8,69 ± 4,50	8,75 ± 4,44	8,09 ± 2,91	10,16 ± 5,12	8,56 ± 3,75[4]
SGOT/SGPT			1,38 ± 0,68	1,99 ± 0,91[3]	1,46 ± 0,75	1,93 ± 0,97[3]	1,55 ± 0,78	1,73 ± 0,78	1,46 ± 0,51	1,71 ± 0,74[3]
GGT (U/L)		57	27,89 ± 19,64	25,27 ± 12,71	31,13 ± 41,16	31,19 ± 46,32	30,75 ± 56,18	34,31 ± 71,67	34,72 ± 44,76[8X2]	34,88 ± 42,45[1X9]
Cholinesterase (U/L)	3930	11500	7785,5 ± 1547,5	7517,7 ± 1582,5[4]	7235,4 ± 1987,2	7425,44 ± 1628,08	7356,2 ± 1668,9	7061,4 ± 1366,8[4]	7178,8 ± 1320,6	7063,3 ± 1075,9
Amylase (U/L)		100	57,03 ± 17,15	56,22 ± 15,92	115,81 ± 317,01	128,16 ± 372,96	59,13 ± 22,08	58,53 ± 22,46	63,88 ± 21,48	62,66 ± 21,72
Lipase (U/L)	7	60	30,22 ± 15,18	27,35 ± 8,30	32,25 ± 14,01	32,09 ± 12,64[5]	31,00 ± 15,38	29,44 ± 14,72	30,59 ± 13,29	28,19 ± 10,31
Trypsin (µg/L)	10	57	44,23 ± 12,81	46,31 ± 10,56	49,19 ± 12,50	52,21 ± 12,78[5]	44,58 ± 10,36	48,49 ± 18,86[4]	43,86 ± 12,36[8]	45,14 ± 11,74[1]
Sodium (mmol/L)	135	145	139,70 ± 3,65	139,89 ± 5,29	137,03 ± 6,99	140,63 ± 1,90[4]	139,75 ± 4,18	140,59 ± 2,56	140,00 ± 2,87	140,63 ± 2,57
Potassium (mmol/L)	3,5	5,1	3,99 ± 0,24	3,97 ± 0,25	3,89 ± 0,36	3,96 ± 0,24	3,86 ± 0,25[7]	3,98 ± 0,21[3]	3,90 ± 0,22	3,89 ± 0,25
Calcium (mg/L)	86	100	91,81 ± 5,35	92,73 ± 5,89	90,69 ± 9,42	93,69 ± 6,40	93,16 ± 4,01	93,31 ± 4,59	94,50 ± 3,32	93,41 ± 4,32[7X8]
Phosphorus (mg/dL)	2,7	4,5	3,60 ± 0,44	3,70 ± 0,43[4]	3,53 ± 0,55	3,65 ± 0,46	3,59 ± 0,43	3,70 ± 0,43	3,62 ± 0,40	3,63 ± 0,44
Cupper (µg/dL)	70	155	91,57 ± 14,43	108,19 ± 16,23[3]	101,50 ± 35,66	111,44 ± 24,69[4]	85, 48 ± 13,75[8X7]	101,81 ± 16,70[3X1]	93,56 ± 15,15[2]	110,63 ± 14,03[3X9]
Magnesium (mg/dL)	1,6	2,5	2,06 ± 0,14	1,95 ± 0,17[3]	1,98 ± 0,22[7]	1,92 ± 0,17	2,05 ± 0,20	1,92 ± 0,14[3]	1,99 ± 0,18[7]	1,92 ± 0,18[4]
Zinc (µg/dL)	50	120	67,59 ± 7,77	75,08 ± 11,00[3]	66,19 ± 10,64	72,63 ± 11,96[3]	64,50 ± 9,80	68,63 ± 8,17[4X5]	63,00 ± 7,34[7]	67,00 ± 9,42[4X5X1]
25-OH-vit. D3 (ng/mL)	6,3	46,4	19,26 ± 7,30	25,43 ± 8,03[3]	17,02 ± 7,21	26,31 ± 5,47[3]	16,76 ± 9,62	25,83 ± 8,40[3]	18,78 ± 9,63	26,21 ± 6,52[3]

LL: Lower limit; UL: Upper limit; [1] $p < 0.05$ versus T12 3 mg Si; [2] $p<0.05$ versus baseline 6 mg Si; [3]: $p<0.01$ versus baseline; [4] : $p<0.05$ versus baseline; [5] : $p<0.05$ versus placebo T12; [6] $p < 0.05$ versus 6 mg Si T12; [7] $p<0.05$ versus baseline placebo; [8] $p<0.05$ versus baseline 3 mg Si; [9]: $p<0.05$ versus T12 6 mg Si; All p-values result from one-tailed t-tests.

Table 3: Urinalysis in women at baseline and after 12 months.

	Normal range		Placebo; n=37		Ch-OSA (3 mg Si);n=33		Ch-OSA (6 mg Si); n=33		Ch-OSA (12 mg Si); n=33	
	LL	UL	Baseline	T12	Baseline	T12	Baseline	T12	Baseline	T12
Urinalysis*										
*Glucose**			0	0	0	1	0	0	0	0
*Proteins**			2	0	0	0	1	0	1	2
*Ketons**			0	0	0	0	0	0	2	0
*Bilirubine**			0	0	0	0	0	0	0	0
*Urobilinogene**			0	0	0	0	0	0	0	0
*Blood**			1	2	0	0	0	0	0	2
*Nitrite**			0	0	0	1	1	0	1	0
*Leucocyte esterase**			16	19	9	12	8	6	13	18
pH	4,6	8	6,49 ± 0,90	6,28 ± 0,71	6,08 ± 0,89	5,83 ± 0,51	6,20 ± 0,76	6,36 ± 0,84	6,00 ± 0,65	5,98 ± 0,66
Urea/creatinine	13,5	32	24,15 ± 7,16	26,41 ± 7,81	24,03 ± 8,22	24,24 ± 9,48	24,69 ± 6,01	24,76 ± 8,32	23,58 ± 7,08	22,13 ± 7,34
Creatinine (g/L)	0,60	1,80	0,63 ± 0,36	0,63 ± 0,41	0,63 ± 0,39	0,77 ± 0,45	0,50 ± 0,29	0,63 ± 0,42	0,66 ± 0,62	0,76 ± 0,63
Uric acid/creatinine	0,23	0,68	0,49 ± 0,20	0,47 ± 0,20	0,45 ± 0,19	0,39 ± 0,21	0,50 ± 0,21	0,43 ± 0,18	0,48 ± 0,25	0,42 ± 0,21
Sodium/creatinine (mmol/g)	90	200	166,09 ± 68,78	168,15 ± 99,21	178,37 ± 109,89	165,28 ± 157,62	171,38 ± 111,23	162,55 ± 100,52	144,02 ± 85,53	118,99 ± 85,45
Potassium/creatinine (mmol/g)	22,7	113,6	78,17 ± 40,39	66,96 ± 33,02	67,20 ± 43,67	54,49 ± 27,96	73,13 ± 46,85	66,05 ± 33,25	66,44 ± 28,54	57,37 ± 27,89
Calcium/creatinine (mg/g)	45	273	169,18 ± 85,86	239,76 ± 130,58	195,61 ± 114,65	268,46 ± 160,38	240,19 ± 136,88	261,81 ± 135,76	198,32 ± 101,83	190,55 ± 113,90
Phosphorus/creatinine	0,36	1,18	0,96 ± 0,31	0,90 ± 0,29	0,96 ± 0,32	0,82 ± 0,31	0,93 ± 0,29	0,81 ± 0,36	0,99 ± 0,26	0,77 ± 0,26
Magnesium/creatinine (mg/g)	64	109	117,32 ± 51,29	125,79 ± 44,99	118,73 ± 57,22	119,54 ± 50,40	131,46 ± 46,21	125,54 ± 54,17	132,52 ± 65,26	110,76 ± 69,66

LL: Lower limit; UL: Upper limit ; * number of patients with parameter present in urine

Table 4: Reasons for drop-out from the study were categorized as "medical" and "non-medical".

Reason to drop out	Detail
Medical reasons	Neuro-endocrine tumor, cancer of liver and pancreas
	Hip pain, eczema
	Cerebro-vascular accident
	Constipation (n=3)
	Allergy to aspartane and vit. D
	Cancer of the breast
	Gal bladder problems, liver cancer
	Idiopathic thrombocytopenia, Severe bruising and purpuric rash
	Hyperthermia, jaundice, nausea, hepatitis
	Feeling unwell while taking study medication
Non-medical reasons	Personal problems, family difficulties, problems with daughter
	Not taken study medication
	No data available of one of the visits
	Dislike the taste of the study medication
	Pregnant
	Transport problems, problem with taxi: not turning up when it should have
	Wrong medication
	Went to Australia, went on holidays
	Taking glucosamine preparation
	Took part in twin trail - prescription Fosomax
	Unable to follow the posology, patient kept forgetting to take the study medication, patient was confused and loosing her memory,…
	Changed her mind and did not want to participate
	Patient couldn't tolerate the taste of the drops while feeling unwell, patient disliked the taste of the medication,…

Table 5: Baseline biochemical parameters in patients who dropped out from the study for medical reasons.

AE / SAE (1)	Group	Pathology	Period drop out (time after inclusion)	Baseline biochemical parameter outside normal range
AE	Placebo	Hip pain, eczema	9 months	*Serum*: Cholesterol increased, HDL low, HDL increased *Urine*: Leukocytes esterase present, Mg increased
AE	Placebo	Hyperthermia, Jaundice, Nausea, Hepatitis	5 months	*Serum*: Cholesterol increased, uric acid increased, LDL increased *Urine*: Leukocytes esterase present, uric acid increased, Ca increased, Mg increased
AE	Ch-OSA 3 mg Si	Constipation	2 weeks	*Serum*: Cholesterol increased, LDL increased, Cu low, Vit D3 low *Urine*: Uric acid increased, Na increased,Ca increased, P increased, Mg increased
AE	Ch-OSA 3 mg Si	Idiopathic thrombocytopenia	4 months	*Serum*: Ferritine low, cholesterol increased, LDL increased, Ca increased, Cu low *Urine*: Leukocytes esterase present, Ca increased, Mg increased
AE	Ch-OSA 3 mg Si	Constipation	6 months	No abnormal values
AE	Ch-OSA 3 mg Si	Allergy to aspartame and vitamin D	3 months	*Serum:* Cholesterol increased, HDL low, LDL increased, trypsin increased *Urine:* Uric acid decreased, urea decreased, Na low
SAE	Ch-OSA 6 mg Si	Neuro-endocrine tumor, cancer of liver and pancreas	7 months	*Serum*: GGT (gamma glutamic transpeptidase) increased, glucose increased, Na low, P increased *Urine*: Uric acid increased, Na increased, Ca increased, K increased, Mg increased
SAE	Ch-OSA 6 mg Si	Breast cancer	8 months	No abnormal values
SAE	Ch-OSA 6 mg Si	Liver cancer, gal bladder problems	3 months	*Serum*: GGT (gamma glutamic transpeptidase) increased, urea increased, P increased, cholesterol increased, LDL increased *Urine*: Uric acid increased, urea increased, Ca increased, P increased, Mg increased
SAE	Ch-OSA 12 mg Si	Cerebro-vascular accident	6 months	*Serum*: GGT (gamma glutamic transpeptidase) increased, cholesterol increased, LDL increased, HDL low *Urine*: Uric acid increased, Na increased, K increased, Mg low
AE	Ch-OSA 12 mg Si	Constipation	6 months	No abnormal values
AE	Ch-OSA 12 mg Si	Feeling unwell while taking study medication	3 months	*Serum:* Uric acid increased, cholesterol increased, HDL low, LDL increased, trypsin increased, Ca low *Urine:* Blood, Nitrite ++, leucocyte esterase +++, Ca low, Mg low

(1) AE: adverse event; SAE: serious adverse event