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**Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline  
in patients with chronic arm lymphoedema and fibrosis after  
surgery and radiotherapy for breast cancer**

Lone Gothard<sup>a</sup>, Paul Cornes<sup>a</sup>, Judith Earl<sup>b</sup>, Emma Hall<sup>c</sup>, Julie MacLaren<sup>d</sup>, Peter Mortimer<sup>e</sup>,  
John Peacock<sup>a</sup>, Clare Peckitt<sup>c</sup>, Mary Woods<sup>d</sup>, John Yarnold<sup>a\*</sup>

<sup>a</sup>Department of Radiotherapy, Royal Marsden Hospital, Sutton, Surrey, UK

<sup>b</sup>Pharmacy Department, Royal Marsden Hospital, Sutton, Surrey, UK

<sup>c</sup>Clinical Trials and Statistics Unit, Institute of Cancer Research, Sutton, Surrey, UK

<sup>d</sup>Lymphoedema Services, Royal Marsden Hospital, Sutton, Surrey, UK

<sup>e</sup>Department of Dermatology, Royal Marsden Hospital, Sutton, Surrey, UK

\* Corresponding author:

John Yarnold, Professor of Clinical Oncology

Academic Radiotherapy Unit, Royal Marsden Hospital

Downs Road, Sutton, Surrey SM2 5PT, UK

Tel: 0044 20 8661 3388 / Fax: 0044 20 8661 3107 / Email: john.yarnold@icr.ac.uk

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arm lymphoedema and fibrosis.

Key words: vitamin E and pentoxifylline, clinical trials, radiotherapy  
complications, lymphoedema, tissue induration, fibrosis.

## **Summary**

### **Background**

Treatment-induced arm lymphoedema is a common and distressing complication of curative surgery and radiotherapy for early breast cancer. A number of studies testing alpha-tocopherol (vitamin E) and pentoxifylline suggest evidence of clinical regression of superficial radiation-induced fibrosis but there is only very limited evidence from randomised trials. Arm lymphoedema after lymphatic radiotherapy and surgery has been used in the present study as a clinical system for testing these drugs in a double-blind placebo-controlled randomised phase II trial.

### **Methods**

Sixty-eight eligible research volunteers with a minimum 20% increase in arm volume at a median 15.5 years (range 2-41) after axillary/supraclavicular radiotherapy (plus axillary surgery in 51/68 (75%) cases) were randomised to active drugs or placebo. All volunteers were given dl-alpha tocopheryl acetate 500 mg twice a day orally plus pentoxifylline 400 mg twice a day orally, or corresponding placebos, for 6 months. The primary endpoint was volume of the ipsilateral limb measured opto-electronically using a perometer and expressed as a percentage of the contralateral limb volume.

### **Findings**

At 12 months post-randomisation, there was no significant difference between treatment and control groups in terms of arm volume. Absolute change in arm volume at 12 months was 2.5% (95% CI -0.40 to 5.3) in the treatment group compared to 1.2% (95% CI -2.8 to 5.1) in the placebo group. The difference in mean volume change between randomisation groups at

12 months was not statistically significant ( $p = 0.6$ ),  $-1.3\%$  (95% CI  $-6.1$  to  $3.5$ ), nor was there a significant difference in response at 6 months ( $p = 0.7$ ), where mean change in arm volume from baseline in the treatment and placebo groups was  $-2.3\%$  (95% CI  $-7.9$  to  $3.4$ ) and  $-1.1\%$  (95% CI  $-3.9$  to  $1.7$ ) respectively. There were no significant differences between randomised groups in terms of secondary endpoints, including tissue induration (fibrosis) in the irradiated breast or chest wall, pectoral fold or supraclavicular fossa, change in photographic breast/chest wall appearance or patient self-assessment of function and quality of life at either 6 or 12 months.

### **Interpretation**

The study fails to demonstrate efficacy of dl-alpha tocopheryl acetate plus pentoxifylline in patients with arm lymphoedema following axillary surgery and lymphatic radiotherapy, nor does it suggest any benefits of these drugs in radiation-induced induration (fibrosis) in the breast, chest wall, pectoral fold, axilla or supraclavicular fossa.

## **Background**

The reversibility of radiation fibrosis in skin and subcutaneous tissues was first suggested by regression of tissue induration (fibrosis) reported in a non-randomised phase II trial by Delanian et al involving intramuscular administration of bovine liposomal Cu/Zn superoxide dismutase (SOD), 5 mg twice-weekly for 3 weeks, to 34 patients with 42 distinct zones of superficial fibrosis [5]. Softening of subcutaneous induration was noted in 86% of fibrotic zones, with an actuarial response rate of 70% by 5 years. Complete regressions were noted in 7/42 (17%) of the fibrotic zones. Supportive data from Perdereau et al included the results of topical applications of SOD over a period of several months in 40 patients with fibrosis after post-mastectomy radiotherapy for early breast cancer [20]. These studies were not pursued after bovine spongiform encephalopathy (BSE) was recognised and bovine products withdrawn.

Experience with alpha-tocopherol (vitamin E), in combination with pentoxifylline is also consistent with a beneficial effect in patients with established fibrosis. A case report by Gottlober et al described marked regression of fibrosis 17 years after postmastectomy radiotherapy in a woman treated with alpha-tocopherol 400 mg once daily and pentoxifylline 400 mg three times daily for several months [14]. In a phase II trial testing alpha tocopherol 500 U twice daily and pentoxifylline 400 mg twice daily for 6 months in 43 patients with marked subcutaneous fibrosis after radiotherapy, regression and functional improvement at 6 months were reported by Delanian et al in all assessable sites of induration [7; 6].

A single case report of a woman treated with pentoxifylline 400 mg three times daily and vitamin E 200 mg twice daily for 18 months reported almost complete healing of an ulcerated radiation-induced fibrosis after therapy for breast cancer [11]. A pilot study testing a

combination of pentoxifylline 800 mg once daily, tocopherol (vitamin E) 1000 IU daily and clodronate reported clinical benefit with more than 50% regression of progressive osteoradionecrosis observed at 6 months in 12 patients [8]. This study included a woman who had developed severe exteriorised osteoradionecrosis following treatment for breast cancer 29 years previously. She had palpable breast fibrosis, including the sternum and a painful fistulous track in the upper part of the bone surrounded by local inflammatory signs, and chronic osteitis with sequestra extrusion. Magnetic resonance imaging showed deep radiation-induced fibrosis below this area without cancer recurrence, and complete bone destruction over an area of  $7 \times 4$  cm. The above combination of pentoxifylline, vitamin E and clodronate was administered for 3 years and was reported as resulting in complete reversal of progressive osteoradionecrosis and the associated radiation-induced fibrosis.

Against this background, a double-blind placebo-controlled randomised phase II study was conducted to test the efficacy of alpha-tocopherol and pentoxifylline in patients with radiation-associated arm lymphoedema. This iatrogenic syndrome was selected because the primary endpoint (arm volume) can be measured optically in an operator-independent manner. In addition, arm lymphoedema continues to cause disability in a minority of patients treated for early breast cancer.

### **Aim**

To test the effects of oral dl-alpha tocopheryl acetate and pentoxifylline in patients with long-standing arm lymphoedema following lymphatic radiotherapy for early breast cancer.

## **Patients and Methods**

### *Eligibility and pre-treatment assessment*

Inclusion criteria included ipsilateral arm lymphoedema following treatment for breast cancer causing  $\geq 20\%$  increase in arm volume, previous radiotherapy treatment to the breast/chest wall plus axilla and/or supraclavicular fossa, freedom from cancer recurrence, availability for follow-up and written informed consent. Pre-treatment baseline assessments included measurement of arm volume using a perometer, clinical assessment of subcutaneous induration within the radiotherapy volume, clinical photographs and patient self-assessments using the EORTC Quality of Life Questionnaires QLQ-C30 and BR23 [10].

### *Antioxidant measurement*

Blood samples were collected from volunteers at baseline and 1-2 weeks before the end of 6 months therapy. Plasma was extracted and stored in liquid nitrogen until it was transferred to King's College for analyses based on the method of Kelly et al using HPLC with ultra-violet detection [16]. Alpha-tocopherol concentration (corrected for internal vitamin E and plasma cholesterol) was measured to assess efficacy of supplementation.

### *Measurement of arm volume*

Arm volumes were measured in an operator-independent manner using a perometer (Model 400T, Pero-System GmbH, Wuppertal, Germany [12; 21]). The volume from wrist to axilla was determined by placing the arm vertically inside a square measuring frame containing rows of infrared light-emitting diodes on two adjacent sides. On moving the frame along the arm, volume was calculated from pairs of diameter measurements every 3 mm, assuming a circular or elliptical cross-section. The volume of the ipsilateral limb was expressed as a percentage of the contralateral (control) limb volume.

### *Clinical assessments*

Clinical examination was undertaken by an oncologist to confirm trial eligibility and to score induration of the breast boost site, pectoral fold and supraclavicular fossa. Induration was scored by palpation using a graded scale (0 = none, 1 = a little, 2 = quite a lot, 3 = very much) and was repeated at follow-up assessments. Response was defined as an improvement of at least 2 grades (e.g. 3 → 1, 3 → 0, 2 → 0) at 12 months post randomisation, considered to represent a clinically worthwhile improvement that could not easily be attributed to measurement error. Clinical photographs were taken of the upper body (hands on hips and above head), but response (change in photographic appearance of irradiated skin or arm at 12 months) was not predefined. Assessments of tissue induration and of clinical photographs were conducted blind to treatment allocation.

### *Quality of life*

The EORTC core questionnaire QLQ-C30 and breast module BR23 were chosen for the study. The core questionnaire QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. The breast module BR23 comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective [10]. Volunteers were asked to continue their usual standard care including hosiery and to complete a set of baseline questionnaires before they started therapy.

### *Trial entry*

Patients were randomised by a member of the Pharmacy Department at the Royal Marsden Hospital via a telephone call to the Clinical Trials and Statistics Unit at the Institute of Cancer Research. Patients were randomised to 6 months of dl-alpha tocopheryl acetate 500 mg twice a day orally plus pentoxifylline 400 mg twice a day orally versus corresponding placebos. Neither the patients nor the investigators were informed of the treatment allocation.

### *Follow-up*

Perometer measurement of arm volumes, clinical assessment and photographs were repeated within 1 week of completing six months of therapy and 12 months after start of treatment. Self-assessments of quality of life were completed at the same intervals plus 3 and 9 months after start of treatment.

### *Endpoints*

The primary endpoint was defined as the percentage change in volume of the ipsilateral arm vs. contralateral arm at 12 months post-randomisation. Secondary endpoints included i) physician assessments of palpable induration and photographic appearance of the breast/chest wall, pectoral fold and/or supraclavicular fossa and ii) patient self-assessments of arm swelling, tissue induration and physical functioning.

### *Sample size*

It was considered that randomisation of 100 patients (50 in each group) would allow detection of a 0.66 standardised difference in percentage change in volume between the treated and

placebo groups with 90% power and 5% significance level (assuming a mean and standard deviation of percentage reduction in volume of approximately 10% and 15% respectively).

### *Analysis*

Change in ipsilateral arm volume was analysed on a continuous scale as the percentage change in excess volume of the swollen arm as a percentage of the contralateral arm at baseline and after therapy. An increase in the difference between the two limbs therefore indicated a deterioration of arm swelling, a decrease meant an improvement in the condition. Change from baseline at 12 months was examined using a t-test. Health status scales were derived from the QoL questionnaires using standard methods [10]. Change in breast induration (palpation) and breast appearance (clinical photographs) were recorded for each individual volunteer. Percentage of patients with a change in induration score of 2 or more were calculated, and comparison between treatment groups assessed by chi-squared test.

## **Results**

### *Patient demographics*

Identification of suitable and interested volunteers took longer than anticipated, and six months before the expiry date of the trial medication we had to close accrual having randomised 68 of our target 100 patients (35 to the treatment group : 33 to the placebo group). This reduced the power of the study from 90% to 85% with a significance level of 10%. The median age of the 68 volunteers (67 female and 1 male) at the start of therapy was 63 years (range 37 to 87). The median time from radiotherapy treatment to vitamin E and pentoxifylline therapy was 15.5 years (range 2 to 41). 33/68 volunteers had wide local excision as part of their primary treatment for breast cancer, and 24 (73%) of these patients had some form of axillary surgery as well. 33/68 underwent mastectomy, and 27 (82%) of

these volunteers had some form of axillary surgery as well. 2/68 volunteers had no primary surgery. The level of axillary surgery performed was described in various terms, including “level 1” and “axillary clearance”, but the exact description was rarely available in the patients’ operation notes. All volunteers had radiotherapy to the breast/chest wall plus axilla and/or supraclavicular fossa (Table 1).

### *Compliance*

Compliance with the treatment protocol appeared to be very high and no side effects from the medication were reported. 63/68 (94%) volunteers completed their trial medication and attended their 6 and 12 months assessments. 1/68 volunteers underwent a hip-replacement at the time of her 6-month assessment, but she completed her trial medication on time and attended her final assessment at 12 months. 66/68 volunteers completed self-assessment questionnaires at baseline, 3, 6, 9 and 12 months post randomisation.

4/68 volunteers were not evaluable at 12 months: 3/35 patients in the treatment arm, 1/33 patients in the placebo arm. One volunteer withdrew from the study after 3 months of therapy because she did not feel she benefited from the trial medication. One volunteer was diagnosed with metastatic breast cancer 4 months after randomisation and was withdrawn. One volunteer completed trial medication but declined her final appointment as she had far to travel and did not feel she had benefited from the trial medication. One volunteer completed trial medication but developed a new primary cancer in the contralateral breast one month prior to her 12-month assessment.

Blood samples were collected at baseline and 1-2 weeks before the end of their 6 months therapy. The laboratory including its storage facilities was relocated during the study period,

and a number of samples were lost. Efficacy of supplementation was therefore assessed in 48/64 (75%) evaluable patients by measuring alpha-tocopherol concentration (corrected for plasma cholesterol) before and after therapy. The results confirm good absorption of drug in individuals randomised to dl-alpha tocopheryl acetate (Table 2).

### *Lymphoedema*

The volume of the swollen arm was expressed as a percentage of the contralateral arm. The primary endpoint was defined as the percentage change in volume of the ipsilateral arm between baseline and 12 months. For example, a reduction in arm volume from 140% at baseline to 130% at 12 months was reported as a 10% reduction in ipsilateral arm volume (it was also reported as a 25% reduction in the degree of arm swelling, an unplanned secondary endpoint). Distribution of arm volume measurements at baseline and 12 months post randomisation is shown in Table 3. Mean change in arm volume in the treatment group was 2.5% (95% CI -0.4 to 5.3); mean change in the placebo group was 1.2% (95% CI -2.8 to 5.1). Mean change for all 64 evaluable patients was 1.8% (95% CI -0.6 to 4.2). The difference in mean volume change between randomisation groups at 12 months was not statistically significant ( $p = 0.6$ ), -1.3% (95% CI -6.1 to 3.5), nor was there a significant difference in response at 6 months, ( $p = 0.7$ ) where mean change in arm volume from baseline in the treatment and placebo groups was -2.3% (95% CI -7.9 to 3.4) and -1.1% (95% CI -3.9 to 1.7) respectively (Table 4).

### *Clinical assessments including tissue induration and clinical photographs*

Secondary endpoints included physician assessments of palpable tissue induration and photographic appearance of the breast/chest wall, pectoral fold and/or supraclavicular fossa.

The results of the serial clinical assessments of induration are shown in Table 5. There was no significant difference in change in tissue induration between the two groups at 12 months. The number of indurated sites recording a response was 6/31 (19%) in the treatment group, and 8/34 (24%) in the placebo group. Clinical photographs were taken at baseline and 12 months post randomisation but did not provide any additional information.

### *Quality of Life*

Quality of Life was assessed as a secondary endpoint using patient self-assessment questionnaires. No significant changes in self-assessed function and quality of life were seen in either of the randomisation groups over the study period (data not shown).

## **Discussion**

The pathophysiology of lymphoedema after radiotherapy and/or surgery involves obstruction of lymphatic flow with consequent imbalance between vascular filtration and lymphatic drainage [1]. Although physical removal of lymphatic vessels at surgery offers a partial explanation, the onset delayed for months or years indicates that this is not the only mechanism. Radiotherapy to the axilla is also a cause of arm lymphoedema, more so after any kind of surgical disturbance [17]. The continuous accumulation and contraction of scar tissue over many years is perhaps the most likely cause of progressive lymphatic obstruction in response to surgery and radiotherapy. Surgical records of affected patients are consistent with this view, describing scar tissue infiltrating and compressing axillary structures, especially the neurovascular sheath. The pathogenesis of surgical scar tissue and radiation fibrosis probably shares much in common in terms of cell and molecular mechanisms. The traditional view regarding radiation fibrosis as the passive remnant of a tissue depleted of cells and beyond effective therapeutic intervention is misleading. More recent models consider radiation

fibrosis in terms of deregulated collagen metabolism [5]. These share features with other fibrotic states characterised by deregulation of collagen deposition and resorption [15]. The significance of these models is that they raise possibilities for reversing established fibrosis.

The effects of hyperbaric oxygen (HBO) therapy offer the strongest clinical evidence in support of healing responses in previously irradiated tissues, including preliminary evidence of a volume response to HBO in radiation-induced arm lymphoedema [19; 18; 13]. In a non-randomised phase II study of 21 patients, a mean 8% reduction in total arm volume at 12 months was recorded using the same techniques as those used in the present study ( $p = 0.005$ ) [13]. Optical volume measurements using a perometer are highly reproducible [12; 21], as the placebo arm of the present study confirms (Tables 3 & 4). The mean 8% reduction in total arm volume achieved by HBO represents a substantially larger proportional reduction in arm swelling. A hypothetical patient with a baseline arm volume of 136% reducing to 128% at 12 months gains a 22% reduction in arm swelling ( $8/36 \times 100$ ). In addition to volume changes, 6/13 evaluable patients in our published study of HBO reported > 25% improvement in  $^{99}\text{Tc}$ -nanocolloid clearance rate from the ipsilateral forearm at 12 months. We therefore consider it highly unlikely that a therapeutic response to alpha-tocopherol and pentoxifylline has been missed.

We have less confidence in the reliability of the physician assessments of radiation-induced induration as secondary endpoints. Tissue induration in the irradiated breast/chest wall, pectoral fold and/or supraclavicular fossa was scored using a graded scale (none, a little, quite a bit, very much). The intention was for assessments to be carried out by the same clinician (JY or PC) before and after antioxidant therapy, but this was not always possible for reasons of availability. However, even when the same observer scored the patient at different time

intervals, significant variation in response was recorded in the placebo arm. Specifically, 6 sites of induration were scored as improved from baseline by  $\geq 2$  grades in the treatment group and 8 sites in the placebo group. Half the placebo responses were generated in patients scored by a single clinician. No worsening of induration was recorded during the trial, and this suggests bias in the observations. In retrospect, this can be explained by the need at follow-up to refer back to pre-randomisation proformas recording the exact areas scored; these proformas included the baseline induration score. Delanian et al recently published a randomised, double-blind placebo-controlled study with a  $2 \times 2$  factorial design testing pentoxifylline and tocopherol in 24 patients with superficial radiation-induced fibrosis [9]. In this positive study, the primary endpoint was a surface measurement of palpable fibrosis. Volume of fibrosis incorporating surface measurements, an ultrasonic measurement of depth and symptom scores according to LENT SOMA scales were included as secondary endpoints. A reduction in mean surface area of fibrosis was recorded as 60% in the treatment group (mean at baseline =  $43.9 \text{ cm}^2$ , at 6 months:  $19.2 \text{ cm}^2$ ,  $n = 6$ ) versus 43% in the placebo group (mean at baseline =  $34 \text{ cm}^2$ , at 6 months:  $19.3 \text{ cm}^2$ ,  $n = 6$ ) together with a decrease in mean volume of fibrosis of 73% in the treatment group (mean at baseline =  $108.9 \text{ cm}^3$ , at 6 months:  $34.3 \text{ cm}^3$ ), versus 51% in the placebo group (mean at baseline =  $84.1 \text{ cm}^3$ , at 6 months:  $31.9 \text{ cm}^3$ ). The significant placebo responses recorded in both double-blinded trials raises serious questions about the continued use of clinical assessment of induration as experimental endpoints.

Our choice of drugs was based on the medication tested in the non-randomised phase II clinical trial by Delanian et al of combined pentoxifylline and tocopherol in 43 patients previously treated with radiotherapy for head and neck or breast cancer who were given pentoxifylline (800 mg/day) and tocopherol (1000 IU/day) for a minimum of 6 months [6].

The present double-blind randomised study was confined to breast cancer patients and the duration of trial medication was limited to six months for all participants. Although the daily doses of medication in the two studies were identical, Delanian et al prescribed natural alpha-tocopherol (*RRR*-alpha-tocopherol), whereas we administered a synthetic form of vitamin E, dl-alpha tocopheryl acetate (*all rac*-alpha-tocopherol). According to the literature, synthetic *all rac*-alpha-tocopherol increases plasma alpha-tocopherol concentrations by only half as much as *RRR*-alpha-tocopherol [2]. In our study, the median plasma alpha-tocopherol level (corrected for cholesterol) increased from 4.9  $\mu\text{M}$  per mmol/cholesterol at baseline to 12.5  $\mu\text{M}$  per mmol/cholesterol at 6 months in the treatment group (Table 2), confirming good compliance with the medication and effective absorption. The increase in plasma alpha-tocopherol levels achieved were at least as great as that reported in two randomised controlled studies reporting highly significant reductions in the rate of pre-eclampsia in pregnant women and improvements in biochemical indices, including increased plasminogen activator inhibitor-1/2 ratio [3; 4]. These trials tested natural vitamin E (400 IU/day) plus vitamin C (1000 mg/day), the latter acting as co-oxidant. Never the less, we consider it extremely unlikely that the use of *all rac*-alpha-tocopherol rather than *RRR*-alpha-tocopherol, offers sufficient explanation for the lack of clinical effects.

In conclusion, this study fails to demonstrate efficacy of *all rac*-alpha-tocopherol and pentoxifylline in patients with radiation-induced lymphoedema. The placebo responses reported in this trial illustrates the difficulty in assessing radiation-induced induration, and highlight the need to identify and validate operator-independent measures of radiation effect.

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Table 1

**Primary nodal therapy including axilla and supra clavicular fossa (SCF) as part of primary treatment for early breast cancer (n = 68)**

Primary nodal therapy for breast cancer	Treatment group	Placebo group	Total
Axillary surgery			
Radiotherapy to axilla and SCF	17	17	34
Radiotherapy to axilla only	8	4	12
Radiotherapy to SCF only	3	2	5
No axillary surgery			
Radiotherapy to axilla and SCF	5	7	12
Radiotherapy to axilla only	1	2	3
Radiotherapy to SCF only	1	1	2
<b>Total</b>	<b>35</b>	<b>33</b>	<b>68</b>

Table 2

**Results from blood samples:  $\alpha$ -tocopherol levels at baseline and after 6 months of treatment corrected for cholesterol (n = 48)**

Treatment group	Baseline		6 months after start of treatment/ placebo tablets	
	Mean (sd) $\mu\text{M}$ per mmol/ cholesterol	Median $\mu\text{M}$ per mmol/ cholesterol	Mean (sd) $\mu\text{M}$ per mmol/ cholesterol	Median $\mu\text{M}$ per mmol/ cholesterol
Treatment (vitamin E* + pentoxifylline) (n = 23)	5.0 (1.02)	4.9 (range 3.5-7.9)	12.2 (5.63)	12.5 (range 4.3-27.8)
Placebo (n = 25)	5.0 (1.22)	4.7 (range 2.9-8.1)	4.6 (1.10)	5.0 (range 2.5-6.8)

\* dl-alpha tocopheryl acetate

Table 3

**Distribution of arm volume (ml) in the ipsilateral and contralateral arm at baseline and 12 months post randomisation (n = 64)**

	Baseline			12 months post randomisation			
	Ipsilateral arm volume at baseline	Contralateral arm volume at baseline	Difference in arm volume at baseline	Ipsilateral arm volume at 12 months	Contralateral arm volume at 12 months	Difference in arm volume at 12 months	Change in arm volume difference at 12 months from baseline
	ml	ml	%	ml	ml	%	%
<b>All</b>							
Mean (sd)	3161.9 (703.0)	2247.0 (407.2)	40.8 (19.1)	3129.4 (707.4)	2197.8 (391.2)	42.6 (21.6)	1.8 (9.5)
Median	2991.5	2112	35.8	2989.5	2170.5	37.1	0.9
Range	1966 – 5124	1539 - 3313	18.7 – 115.8	2044 - 5498	1448 - 3316	12.7 – 133.0	-18.1 – 33.7
<b>Placebo</b>							
Mean (sd)	2976.8 (660.3)	2127.6 (379.9)	40.5 (21.7)	2940.7 (668.9)	2087.5 (374.2)	41.7 (24.2)	1.2 (10.9)
Median	2786	2047.5	35.7	2755.5	2037.5	37.1	-2.3
Range	2327 – 5124	1550 - 3264	18.7 – 115.8	2044 - 5498	1448 - 3297	12.7 – 133.0	-18.1 – 33.7
<b>Treatment</b>							
Mean (sd)	3346.9 (705.5)	2366.3 (404.0)	41.1 (16.4)	3318.0 (704.2)	2308.0 (381.9)	43.6 (18.9)	2.5 (8.0)
Median	3217.5	2312.5	36.5	3260.5	2218	36.6	2.9
Range	1966 – 4893	1539 - 3313	19.8 – 83.0	2127 - 5167	1670 - 3316	19.8 – 84.2	-10.9 – 23.5

Table 4

**Distribution of arm volume (ml) in the ipsilateral and contralateral arm at baseline and 6 months post randomisation (n = 63\*)**

	Baseline			6 months post randomisation			Change in arm volume difference at 6 months from baseline
	Ipsilateral arm volume at baseline	Contralateral arm volume at baseline	Difference in arm volume at baseline	Ipsilateral arm volume at 6 months	Contralateral arm volume at 6 months	Difference in arm volume at 6 months	
	ml	ml	%	ml	ml	%	
<b>All</b>							
Mean (sd)	3160.9 (708.9)	2245.4 (410.3)	40.9 (19.3)	3089.7 (747.7)	2228.3 (434.6)	39.2 (22.0)	-1.67 (12.0)
Median	2985	2208	35.4	2842	2154	36.2	-2.14
Range	1966 – 5124	1539 – 3313	18.7 – 115.8	1997 – 5453	1461 – 3435	-24.9 – 112.5	-56.8 – 18.8
<b>Placebo</b>							
Mean (sd)	2976.8 (660.3)	2127.6 (379.9)	40.5 (21.7)	2910.6 (644.7)	2101.2 (386.2)	39.4 (22.0)	-1.12 (7.74)
Median	2786	2047.5	35.7	2748.5	2028	36.7	-3.32
Range	2327 – 5124	1550 – 3264	18.7 – 115.8	1997 – 5201	1461 – 3168	7.77 – 112.5	-11.7 – 17.9
<b>Treatment</b>							
Mean (sd)	3350.9 (716.8)	2367.1 (410.6)	41.2 (16.7)	3274.7 (810.1)	2359.5 (448.6)	39.0 (22.4)	-2.25 (15.4)
Median	3210	2282	35.4	3154	2189	35.5	-0.82
Range	1966 – 4893	1539 - 3313	19.8 – 83.0	2125 - 5453	1717 - 3435	-25.0 – 88.2	-56.8 – 18.8

\* 1/64 patients evaluable at 12 months did not attend assessment at 6 months.

Table 5

**Change in induration score of fibrosis of 2 grades or more by randomisation (n = 64)**

Induration	All patients	Placebo	Treatment	P-value
Site 1	6 / 37 = 16.2	4 / 20 = 20.0	2 / 17 = 11.8	0.45
Site 2	8 / 28 = 28.6	4 / 14 = 28.6	4 / 14 = 28.6	1.00

There is no significant difference between randomisation groups, p = 0.45 (site 1) and p = 1.00 (site 2).