Journal of Plastic, Reconstructive & Aesthetic Surgery xxx (xxxx) xxx-xxx

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Lymfactin® gene therapy with vascularized lymph node transfer reduces compression-free swelling and enhances quality of life in breast cancer-related lymphedema: Final Phase I trial results

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Received 6 July 2025; Accepted 8 October 2025

KEYWORDS
Breast cancer-related lymphedema;
BCRL;
Microvascular lymph node transfer;
Breast

Summary *Background:* Lymfactin® is a gene-therapy vector encoding vascular endothelial growth factor C designed to promote lymphatic vessel growth. It is administered during vascularized lymph node transfer (VLNT) to treat breast cancer-related lymphedema. This study presents the final efficacy and long-term safety results of the Lymfactin® Phase I trial.
Methods: Between 2016 and 2018, 12 patients with breast cancer-related lymphedema received a therapeutic dose of Lymfactin® injected into the VLNT flap with or without autologous breast reconstruction. Patients were followed up annually for 4 years.

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https://doi.org/10.1016/j.bjps.2025.10.013

reconstruction;
Gene-therapy

Results: The mean seven-day swelling volume, defined as the volume change after one week of compression interruption, decreased clearly compared to baseline at the three-year follow-up: 105.7 ± 161.0 ml vs. 14.9 ± 174.2 ml. The total lymphedema quality of life (LQOLI) scores improved significantly from baseline to the three-year follow-up ($p = 0.02$). Within the LQOLI subdomains, physical ($p < 0.01$) and psychosocial ($p = 0.01$) scores showed significant improvement over 3 years postoperatively. Six of the 12 participants reduced or discontinued compression garment use within 3 years postoperatively. This group exhibited significantly smaller upper extremity volume differences than those who continued regular compression use (317.8 vs. 923.2 ml, $p = 0.04$). No serious adverse events were reported, and all the patients remained alive during the four-year follow-up.

Conclusion: This prospective multicenter study demonstrated that Lymfactin® with VLNT is safe and well tolerated. Although volume reduction was most evident in the first year, half of the patients reduced or discontinued compression use, and quality of life improved over long-term follow up.

Breast cancer-related lymphedema (BCRL) affects over 20% of patients undergoing axillary lymph node dissection and possible radiation therapy for metastatic breast cancer.[1] Although a completely curative treatment for BCRL is lacking, surgical options, such as vascularized lymph node transfer (VLNT), may restore lymphatic function and significantly alleviate symptoms in selected patients.

Vascular endothelial growth factor C (VEGF-C), a key regulator of lymphangiogenesis, induces lymphatic vessel growth and reduces edema.[2,3] VEGF-C introduction triggers local factor production, driving capillary growth within 2 weeks.[4] However, immune-mediated adenoviral vector clearance reduces gene expression and partially reverses this effect.[5] Within six months, new vessels mature into functional collecting lymphatics. Preclinical models have shown positive outcomes with VEGF-C-based therapies, including restoration of lymphatic networks in damaged tissues.[6–9]

Lymfactin® is a gene-therapy vector based on adenovirus type 5 that is designed to locally express human VEGF-C.[10] It rectifies deficient lymphatic flow by fostering the growth and repair of the lymphatic vessels. When used in conjunction with VLNT, it aids in the integration of the transferred lymph nodes into pre-existing lymphatic vessel network. This article presents the final efficacy and safety outcomes of the Lymfactin® Phase I trial, which combined VLNT surgery and adenoviral VEGF-C treatment (Lymfactin® treatment).

Methods

Study protocol

The study was approved by the Finnish Medical Agency and the Helsinki Hospital District Ethics Committee (ClinicalTrials.gov, ID: NCT02994771).

This first-in-human Phase I, open-label, uncontrolled dose-escalation study was conducted between 2016 and 2018 at university hospitals in Turku, Helsinki, and Tampere, Finland. The primary objective was to evaluate the safety, tolerability, and biodistribution of a single dose of Lymfactin® in patients with BCRL. This gene therapy was administered during VLNT surgery with or without deep inferior epigastric artery perforator (DIEP) breast reconstruction. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Operative technique and administration of Lymfactin®

A VLNT flap, with or without combined DIEP breast reconstruction, was performed following an established procedure.[11] Lymfactin® was injected into 2 to 4 sites in the flap, avoiding the pedicle, and vascular anastomoses were completed as previously described.[10] The original study comprised 2 dose cohorts: 3/15 patients received a lower dose (1×10^{10}), and 12/15 patients received a therapeutic dose (1×10^{11}) of viral particles, as previously reported.[10] Only the therapeutic dose cohort was included in this study. Reverse lymph node mapping was used to minimize the risk of donor site lower extremity lymphedema.[12]

Study visits and data collection

Baseline and efficacy results are reported up to 3 years, with safety follow-up extended to 4 years. The detailed first-year data, including multiple laboratory and clinical follow-up visits, have been published previously[10,13] and are not repeated here (Supplemental Figure 1). The baseline data included demographic information and medical history, including breast cancer and BCRL. Patients underwent screening with ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT), followed by annual chest and abdominal CT scans for 4 years. A phone interview was conducted 4 years postoperatively to evaluate long-term outcomes and safety. Lymphoscintigraphy was performed at baseline and annually for up to 3 years.[14,15]

Table 1 Demographic characteristics of 12 patients who received Lymfactin® (1×10^{11} vp in 2 ml) in conjunction with a VLNT procedure between 2016 and 2018. Patients were divided into two groups according to whether they used a compression sleeve regularly for three years postoperatively or had reduced or discontinued its use. *p*-values denote the comparison between the two groups.

	All patients (n=12)	Patients who used compression garment regularly at three-year post-op (n=6)	Patients who reduced or discontinued using compression garments at three-year post-op (n=6)	p-value*
Age (years)	55.5 ± 6.7	53.5 ± 6.4	57.5 ± 6.9	0.32
BMI (kg/m^2) at baseline	27.8 ± 3.7	29.2 ± 3.0	26.3 ± 4.1	0.20
BMI (kg/m^2) at one-year post-op	27.7 ± 3.9	29.0 ± 4.0	26.3 ± 3.8	0.26
Duration of BCRL (months)	28.2 ± 10.7	27.8 ± 13.9	28.5 ± 7.5	0.92
TI at baseline	28.8 ± 15.3	28.5 ± 13.0	29.0 ± 18.5	0.96
TI at three years post-op	22.8 ± 18.0	29.5 ± 18.0	16.1 ± 16.7	0.21
VLNT treatment without breast reconstruction	4 (33.3)	2 (33.3)	2 (33.3)	0.73
VLNT treatment with breast reconstruction	8 (66.7)	4 (66.7)	4 (66.7)	

BMI, Body mass index; TI, Transport Index.
Values are reported as mean ± SD, except for the number of patients marked as (n (%).
* Statistical significance was set at $p < 0.05$.

Safety assessments included routine hematology, clinical chemistry tests, and urinalysis performed at baseline and annually for up to 3 years postoperatively (Supplemental Tables 1 and 2).

Adverse events (AEs) were collected from baseline to the last visit and recorded in the case report form. They were graded according to the Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03). All AEs, irrespective of causality, were documented during the first postoperative year[10]; thereafter, only treatment-related events were recorded. Serious adverse events (SAEs) were defined using the International Conference on Harmonization criteria, reported within 24 h, and assessed for causality by the investigator. Patients with unresolved AEs were followed until resolution or no further medical follow-up was indicated. Safety data collection adhered to the Sponsor's or Clinical Research Organisation's Standard Operating Procedures, in compliance with EU regulations. SAE reporting followed the study-specific SAE management plan.

Volume measurements of extremities

Trained staff measured the upper and lower extremity volumes of the patients using the Brorson's method.[16] The total volume of both upper extremities was recorded, and the difference was calculated as the excess volume. Excess volume was measured immediately after removing the compression garment and documented at baseline and annually for up to 3 years (Supplemental Figure 1). The mean seven-day swelling volume was defined as the excess volume change after one week of compression interruption. Compression garment use was continued until the next follow-up.

After one year, patients could reduce or discontinue compression use if they observed improved swelling symptoms. For those who discontinued entirely, the volume was subsequently measured without compression at years 2 and 3. Lower extremity volumes were measured annually, and a negative value indicated that the donor extremity was smaller than the contralateral extremity.

Lymphedema quality of life inventory

Patients completed the Lymphedema Quality of Life Inventory Questionnaire (LQOLI)[17] at baseline and annually for up to 3 years. The questionnaire assesses the quality of life in 3 domains—physical, psychosocial, and practical—along with a total score. The LQOLI includes 45 self-administered questions, with a maximum score of 123, with a lower score indicating better QoL.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 29.0 (IBM® Corporation, NY, USA) and GraphPad Prism 10.4 (GraphPad Software, Inc., CA, USA). Data normality was assessed using the D'agostino-Pearson normality test. Non-normally distributed data are reported as median and interquartile range (IQR). Volumetric data were compared between baseline and study visits using the Wilcoxon

Table 2 Preoperative demographics and volume excess between affected and no affected upper extremities measured with and without a compression garment at baseline and three-year postoperatively.

Patient number	Age (y)	BMI[a] (kg/m^2) at baseline	Duration of lymphedema (months)	Volume excess with compression garment at baseline (ml/%)	Volume excess without compression garment at baseline (ml/%)	Volume excess with compression garment at three-year post-op (ml/%)	Volume excess without compression garment at three-year post-op (ml/%)	TI[b] of the affected arm at baseline	Ti of the affected arm at three-year post-op	Using compression garment regularly at three-year post-op
1	66	24	18	667/38	710/39	518/28	623/35	45	45	no[c]
2	48	31	28	491/27	487/27	-	575/30	14	0.2	no
3	64	24	40	88/5	185/10	-	207/13	3	14	no
4	58	30	52	938/41	1357/ 61	898/35	1095/43	18	19	yes
5	56	32	28	380/14	290/11	-	252/11	45	16.8	no
6	59	25	33	84/4	286/15	-	99/5	45	22	no
7	44	26	36	232/10	285/13	398/17	466/21	19	42	yes
8	54	26	19	160/9	184/12	142/9	160/10	45	0.2	yes
9	62	33	22	737/30	937/39	1261/52	1444/57	19	26	yes
10	52	22	24	181/12	292/19	398/17	151/10	22	12.2	no[c]
11	54	28	24	1617/84	1950/106	1874/92	1568/84	45	45	yes
12	49	32	14	750/30	626/26	1127/42	806/27	25	45	yes

[a] Body mass index;
[b] Transport index;
[c] As the compression garment was used intermittently or only during daytime, measurements with the garment applied were also collected.

matched-pairs signed-rank test. Comparisons between compression garment users and non-users were analyzed using the Student's *t*- and Mann-Whitney *U* tests. Repeated measures analysis of variance (ANOVA) was used to compare follow-up time points with baseline measurements to analyze the LQOLI, transport index (TI), and volume change of the lower extremities. Statistical significance was set at $p < 0.05$.

Results

Table 1 summarizes the demographic characteristics of all 12 patients who received a therapeutic dose of Lymfactin® (1×10^{11} vp in 2 ml), whereas Table 2 depicts per-patient demographic information. Further baseline details can be found in the articles by Hartiala et al. in 2020[10] and Leppapuska et al. in 2022.[13]

Excess volume with a compression garment

Volume measurements were unavailable for one participant on the two-year visit but were available on the three-year visit.

At baseline, the median volume excess with compression was 435.5 ml (IQR 165.3–746.8 ml), corresponding to 20.6% (IQR 9.4–36.1%). One-year postoperatively, this decreased significantly to 239.5 ml (IQR 54.5–643.8 ml), 9.4% (IQR 3.3–34.0%), ($p = 0.03$). At 2 years post-op (9/12 patients), the median excess volume increased to 564.0 ml (IQR 77.0–977.5 ml), 26.2% (IQR 4.3–37.7). By 3 years (8/12 patients), the median excess volume was 708.0 ml (IQR 206.0–1227.5 ml), 31.4% (IQR 11.0–49.1%), including only patients who continued compression usage (Figure 1A).

Excess volume without a compression garment

The median excess volume at baseline without compression was 390.0 ml (IQR 285.3–880.3 ml), 22.4% (IQR 11.8–39.0%), and at one year-post-op it was 487.0 ml (IQR 104.8–813.8 ml), 18.5% (IQR 6.2–41.3%). At the two-year study visit, measurements were conducted on 10/12 with a volume excess of 428.0 ml (IQR 128.5–1151.8 ml), 20.5% (IQR 7.6–42.7%) and 12/12 at three-year post-op, 520.5 ml (IQR 171.8–1022.8 ml), 24.1% (IQR 10.1–40.8%), without significant differences compared to baseline (Figure 1B).

Seven-day swelling volume

At baseline, the mean seven-day swelling volume (week of compression interruption) in 12 patients was 105.7 ± 161.0 ml, with a statistically significant difference ($p = 0.04$) between excess volume with and without compression garments (Figure 2A). At one-year post-op, it was 84.4 ± 143.0 ml ($p = 0.07$) among the 12 patients. At 2 years post-op, it was 94.3 ± 114.8 ml ($p = 0.07$) in 7/12 patients, and at three-year post-op, it decreased to 14.9 ± 174.2 ml ($p = 0.82$), in 8 /12 patients (Figure 2B).

Lymphoscintigraphy

The mean TI of the affected upper extremity was 28.8 ± 15.3 at the baseline, 26.6 ± 19.7 at one-year post-op, 25.3 ± 16.9 at two-year post-op, and 23.9 ± 16.8 at three-year post-op, without any significant difference between the study visits ($p = 0.81$; Figure 3). The mean change in the TI over 3 years was -4.8 ± 20.1, ranging from −44.8 to 23.0.

Lymphedema quality of life inventory

Substantial morbidity associated with BCRL was observed at the baseline. The median total LQOLI score at baseline was 41.0 (IQR 28.5–75.5) and showed statistically significant improvement at each annual follow-up: 25.5 (IQR 14.3–41.8) at one year, 18.0 (IQR 12.0–43.0) at two- year, and 18.0 (IQR 7.0–48.5) at three-year (Figure 4A).

When comparing changes in the 3 LQOLI domains from baseline to a three-year follow-up, a significant improvement was observed in the median physical domain score, which decreased from 16.5 (IQR 9.3–20.8) to 6.5 (IQR 2.5–14.3)($p < 0.01$). In the psychosocial domain, it decreased from 13.0 (IQR 9.8–24.0) to 5.50 (IQR 1.0–12.8)($p = 0.01$; Figure 4B-C). In the practical domain, a significant

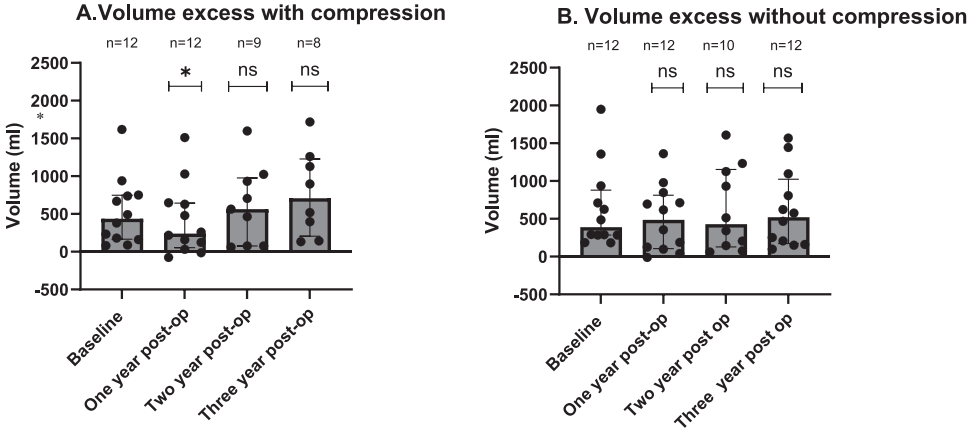

Figure 1 A-B. Median volume excess between the upper extremities with and without compression. A. Volume excess with compression garments differs statistically between the baseline and one-year postoperatively (*$p = 0.03$). B. There was no statistically significant volume excess between baseline and study visits when compression garments were not used. Data are shown as median and interquartile range.

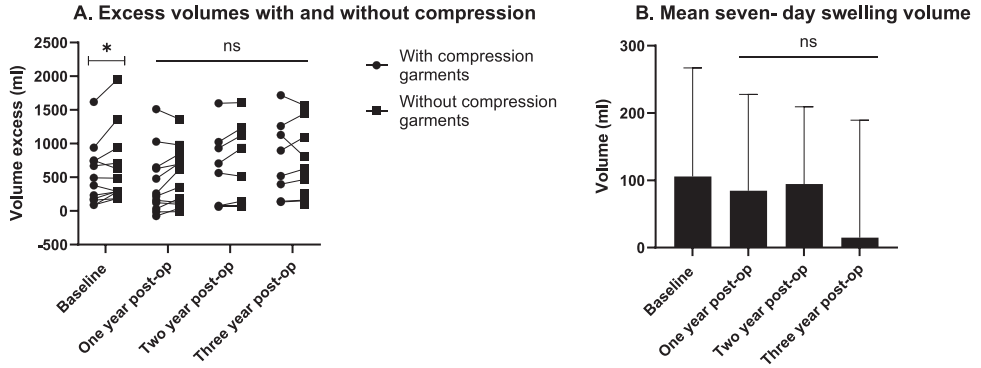

Figure 2 A-B. Seven-day swelling volume with and without compression. A. At baseline and one-year post-op visits, seven-day swelling volume was measured for all 12 participants. At baseline, the volume excess difference between with and without compression was significant (*p = 0.04), but this difference was no longer significant after follow-up visit measurements. B. The mean seven-day swelling volume at the follow-up visits. At baseline, the seven-day swelling volume was 105.7 ± 161.0 ml, and at three-year postoperatively, it was 14.9 ± 174.2 ml.

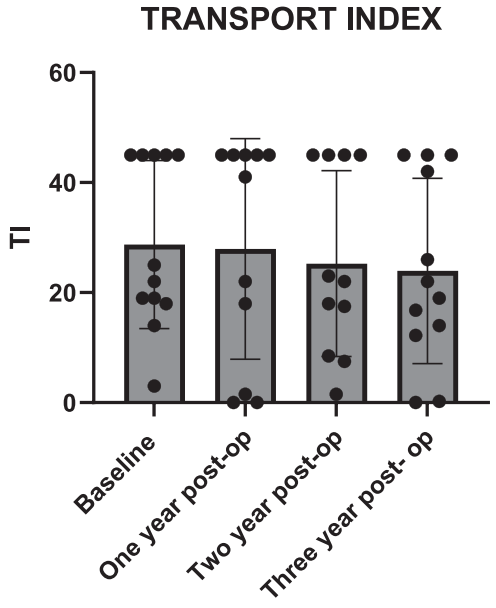

Figure 3 Transport index measured at baseline and study visits. There was no significant difference between study visits (p = 0.81). Data are shown as mean ± SD. TI, transport index.

improvement was observed at the one-year follow-up from 15.50 (IQR 8.50-26.50) to 9.0 (IQR 4.30-13.50)(p < 0.01), but no statistically significant differences were observed in the three-year follow-ups compared to baseline from 15.50 (IQR 8.50-26.50) to 4.50 (IQR 3.1-15.8)(p = 0.13; Figure 4D).

Compression garments

At 2 years post-op, 5/12 (41.7%) patients had reduced or discontinued the use of compression garments. By 3 years, this increased to 6/12 (50.0%); 4 had discontinued use entirely, and 2 wore them only during the day (Table 2). One patient resumed use after having discontinued at two-year post-op.

There were no significant differences between those who regularly used compression garments and those who had reduced or discontinued its use in terms of age (p = 0.32), BMI at baseline (p = 0.20), duration of BCRL (p = 0.92), TI at baseline (p = 0.96), or TI at 3 years post-op (p = 0.21; Table 1). Over the three-year follow-up, TI decreased by 10.7 units in patients who no longer used compression garments regularly, while it increased by 1.0 unit in those who continued regular use; however, the difference was not statistically significant (p = 0.34).

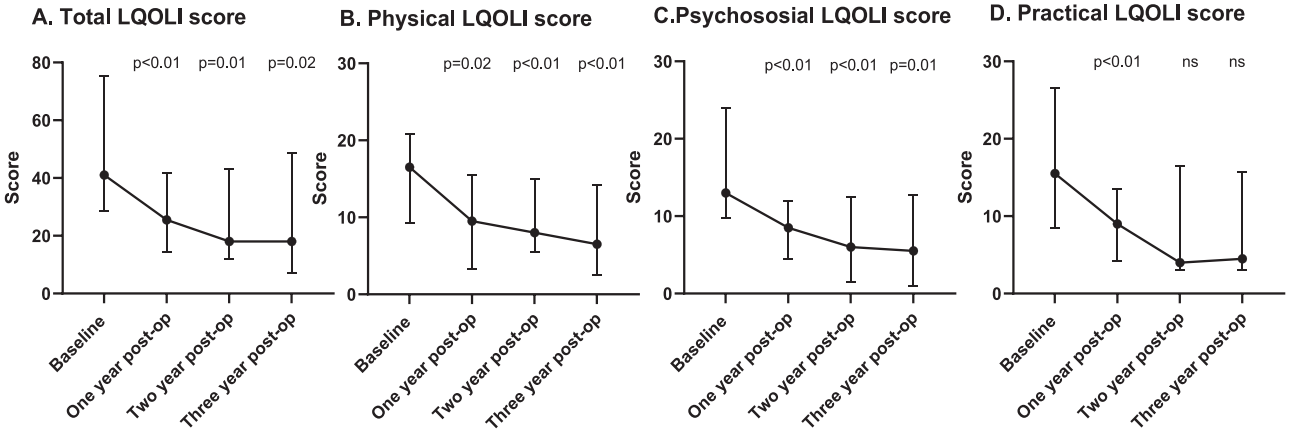

Figure 4 A-D. Quality of life assessment was conducted using the LQOLI questionnaire. A lower score represents a better quality of life. The p-values indicate the statistical significance of the difference in LQOLI scores compared to baseline scores. Data are shown as median and IQR.

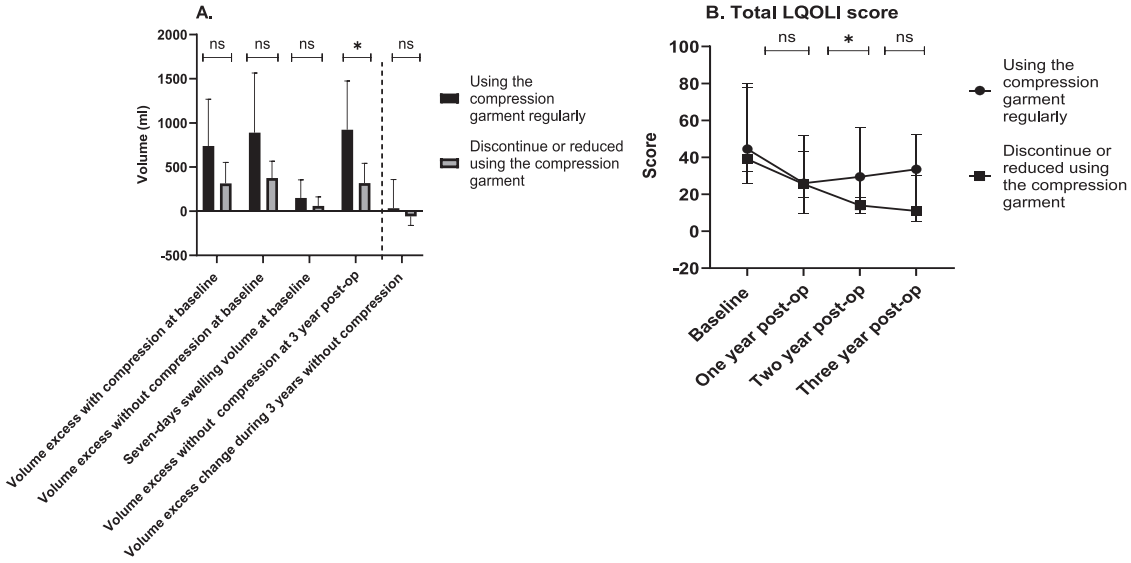

Figure 5 A-B. Comparison of two groups (n = 6 in both groups) based on regular compression garment usage (23 h/day) at three years after the operation. A. Volume excess difference between the groups. There was a significant difference in volume excess without a compression garment at three years post-op between the groups (*p = 0.04) B. The total LQOLI scores of the two groups are based on whether the compression garment is used regularly for 23 h per day for three years after surgery. The interaction between study visits and compression use was mostly non-significant, except between one and two-year post-op visits (*p = 0.05).

Figure 5A shows that at baseline, volume excess was higher in participants who continued compression garment use for 3 years, both with (739.0 ± 529.7 ml vs. 314.7 ± 238.1 ml, p = 0.10) and without (889.8 ± 675.0 vs. 375.2 ± 191.2, p = 0.10) garment, though the difference was not statistically significant. At 3 years post-op, there was a statistically significant difference in excess volume without compression garments between the patients who continued using compression and those who discontinued or reduced their use (923.2 ± 551.7 ml vs. 317.8 ± 224.3 ml, p = 0.04).

When comparing the effect of regular compression garment use on changes in total LQOLI scores over three-year post-op, Figure 5B shows that the interaction between study visits and compression use was mostly non-significant, except for the effect between one and two-year post-op visits (p = 0.05). The LQOLI improved in both groups up to one year after surgery. Among those who reduced their compression use, LQOLI continued to improve beyond this point, whereas among those who continued regular compression use, LQOLI declined after the first year.

Volume measurements and clinical symptoms of the donor limb

The mean volume difference between donor and non-donor extremities was −94.5 ± 300.2 ml at baseline and −209.0 ± 351.1 ml at three-year post-op (p = 0.15; Figure 6). None of the participants showed clinical signs of secondary lymphedema of the lower extremities during the follow-up period.

CT scan

During the three-year follow-up, 2 participants were diagnosed with metastatic breast cancer. One patient experienced 3 episodes of facial nerve palsy over a two-year period. Suspected

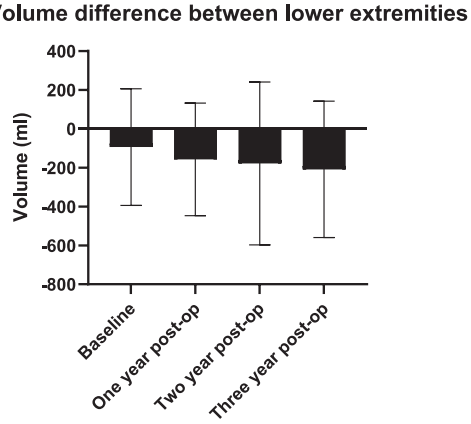

Figure 6 Mean volume difference between the donor and non-donor lower extremities. A negative value indicated that the measured volume of the donor-site extremities was smaller than that of the non-donor extremity. There was no measurable edema of the donor extremity. Data are shown as mean and SD.

liver metastasis detected on a three-year follow-up CT scan was confirmed using MRI, and skull bone metastasis was identified at the four-year follow-up. The patient received radiation therapy on the brain and skull. Another participant, who had received a lower dose of Lymfactin® (1×10^{10}), was diagnosed with metastasis in the T8 vertebral body during a three-year postoperative full-body CT scan. A follow-up CT scan 2 months later showed disease progression, and treatment with palbociclib (Ibrance®) and letrozole (Letrozole®) was initiated.

Safety profile

The one-year safety study was completed using the maximum planned dose of Lymfactin®, with no dose-limiting

toxicities or SAEs reported during the first 2 years[10,13] Laboratory tests performed at baseline and annually revealed no clinically significant abnormalities over the three-year period (Supplemental Tables 1 and 2). No SAEs were observed during the three-year follow-up, and all AEs after year 2 were deemed unrelated to the study. All patients remained alive and free of new malignancies at the four-year follow-up.

Discussion

This study reports the final three-year efficacy and four-year safety results of a Phase I multicenter trial combining Lymfactin® gene therapy with VLNT in patients with BCRL. The results indicate that following Lymfactin® treatment, the volume change in the upper extremities during a seven-day compression interruption was smaller (14.9 ± 174.2 ml) 3 years after surgery compared to preoperative measurements (105.7 ± 161.0 ml), indicating disease stabilization following surgery. In addition, the total LQOLI scores improved significantly from baseline and the improvement was sustained at the three-year follow-up, with the physical and psychosocial domains showing sustained improvements over time. Although the mean upper extremities volume differences did not decline, 6/12 patients reduced or discontinued compression use. Lymfactin® was well tolerated in the long-term, with no serious VEGF-C-related AEs reported.

This study showed that, despite wide baseline differences in upper extremity volumes, the volume change during a seven-day compression-free period significantly decreased over the 3 periods. Before treatment, fluid accumulation without compression was notable (105.7 ± 161.0 ml, $p = 0.04$), highlighting the importance of compression garment therapy. By year 3, swelling during the same period was minimal (14.9 ± 174.2 ml) and no longer statistically significant ($p = 0.82$), suggesting improved lymphatic function. In this context, the long-term reduction in short-term swelling fluctuations observed in our cohort, even during compression discontinuation, suggests that Lymfactin® treatment and axillary scar release may have contributed to stabilizing lymphatic function in chronic BCRL. Supporting this interpretation, prior studies have shown that without intervention, BCRL typically progresses with worsening edema and fibrosis.[18,19] Blom et al. reported a sixfold lower risk of progression at 6 months in patients using compression garments than in those without.[18] Notably, in some patients, removal of the compression garment did not increase excess volume; instead, it decreased. Although the mechanism is not fully understood, one possibility is that removing the compression garment increased the use of the affected extremity and facilitated fluid clearance. Despite efforts to standardize compression, inter-individual differences in its effectiveness likely remain. Nevertheless, at the population level, a statistically significant reduction in the seven-day swelling volume was observed compared with baseline.

BCRL symptoms, such as heaviness, pain, tightness, weakness, and infections, negatively impact QoL,[20-22] whereas VLNT is known to improve QoL by reducing swelling.[23-25] Gratzon et al. reported a significant increase in lymphedema-specific QoL scores ($p < 0.001$) one year after VLNT,[26] and De Brucker et al. found improvements across the physical, psychosocial, and social domains ($p < 0.001$).[23] Unlike earlier studies with shorter or inconsistent follow-up periods, our study used the LQOLI questionnaire annually for a three-year period. We found that Lymfactin® treatment significantly improved total LQOLI scores within the first year, with benefits maintained throughout the third year ($p = 0.02$). When examining the subdomain LQOLI scores, physical ($p < 0.01$) and psychosocial ($p = 0.01$) scores were significantly better 3 years after the procedure than before. Interestingly, patients who reduced compression use after year one reported better LQOLI scores at 3 years than those who continued using it regularly, suggesting a link between symptom relief and improved QoL.

This study demonstrated a significant reduction in upper extremity volume difference during the first postoperative year with compression garments (435.5 ml to 239.5 ml, $p = 0.03$). However, no further improvement was observed thereafter, and the volume began to increase. The initial reduction was attributed to the removal of excess lymphatic fluid before stabilization. The subsequent increase may reflect the natural course of chronic lymphedema, where soft tissue remodeling and fibrofatty tissue accumulation become predominant in the later stages. Given the wide variation in baseline BCRL severity (excess volume 5–84%) and likelihood of fibrofatty changes in advanced cases—changes that are unresponsive to compression and not reversed by VLNT—full normalization is unlikely, as VLNT is most effective in early-stage lymphedema and does not target fibrofatty tissue.[11,27,28] Previous studies have suggested that combining VLNT with liposuction can improve the outcomes in such patients.[29,30] However, liposuction was not included in this study.

Participants wore compression garments for one year postoperatively, after which their use could be reduced based on symptom relief. The results showed that upper extremity volume differences began to increase after one year, suggesting that compression may be required for at least 2 years to maintain treatment benefits. At 3 years, only half of the participants continued using regular compression. Those who continued had larger preoperative volume differences (889.8 ml vs. 375.2 ml) and significantly greater volume differences at the three-year follow-up (923.2 ± 551.7 ml vs. 317.8 ± 224.3 ml, $p = 0.04$). This finding supports the theory that fibrofatty changes are present in patients with greater baseline swelling. This interpretation is further supported by the fact that all patients enrolled in the trial were required to have effective compression therapy at the time of screening, which meant that upper extremity swelling with pitting edema was not permitted. Additional support for this interpretation comes from the observation that some of these patients underwent liposuction after discontinuing the trial, which resulted in fibrotic adipose tissue. Overall, these findings suggest that VLNT is most effective in patients without advanced tissue changes, who are consequently more likely to reduce compression garment use postoperatively.

Two out of 12 patients (16.7%) developed distant metastases—one in the liver and brain and the other in the bones, which are common sites for breast cancer spread.[31]

These cases were likely due to the natural progression of breast cancer rather than the long-term oncological effects of Lymfactin® treatment. The five-year survival rate for early-stage breast cancer exceeds 90% but drops to 26% in de novo metastatic cases.[32] Approximately 20–30% of patients with breast cancer develop distant metastases, and 3.5% present with them at diagnosis.[33] Patients with high-risk disease were excluded from the study. Metastases were detected using CT imaging, as outlined in the study protocol. Notably, no deaths or new malignancies occurred during follow-up, except for one case of basal cell carcinoma diagnosed within one year of the procedure.

This study has some limitations. The cohort size was relatively small, which may have limited the statistical power and generalizability of the findings. Efficacy data were obtained without a control group, making it impossible to separate the effects of VLNT from those of Lymfactin® in this Phase I trial, as all patients received both treatments. Notably, although median values change, the IQRs overlapped substantially, which may reflect population heterogeneity and small sample size, limiting statistical power and may mask clinically relevant differences. Finally, it is important to recognize that BCRL is a multifocal disease in which lymphangiogenesis alone may not be sufficient in the late stages of disease progression as it involves tissue scarring and fatty changes that this approach cannot fully reverse.

Conclusion

The combination of Lymfactin® gene therapy with VLNT appears safe and well tolerated over a four-year period, with no serious VEGF-C-related AEs. Although overall volume did not consistently decline, patients experienced reduced fluctuations and improved QoL. Half of them could reduce or discontinue compression, supporting the feasibility of combining gene therapy with microsurgery for lymphatic regeneration in BCRL. Although the trial ended early due to inconclusive Phase II results, these findings offer a valuable foundation for future studies across different stages of lymphedema.

Ethical approval

The research protocol was approved by the Ethical Committee of the Helsinki University Hospital. Clinical trial-gov NCT02994771.

Funding

The Lymfactin® phase I was supported by Herantis Pharma Plc. (Espoo Finland).

Declaration of Competing Interest

PH, SS, ES, IK, JK, TV, OL and AS have received honoraria for participating in advisory boards of Herantis Pharma Plc. (Espoo, Finland), which was responsible for trial management. The authors do not have financial disclosures to report.

Acknowledgements

We wish to thank the patients participating in this study, the study nurses, and operating room and plastic surgery ward personnel at all participating centers.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bjps.2025.10.013.

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