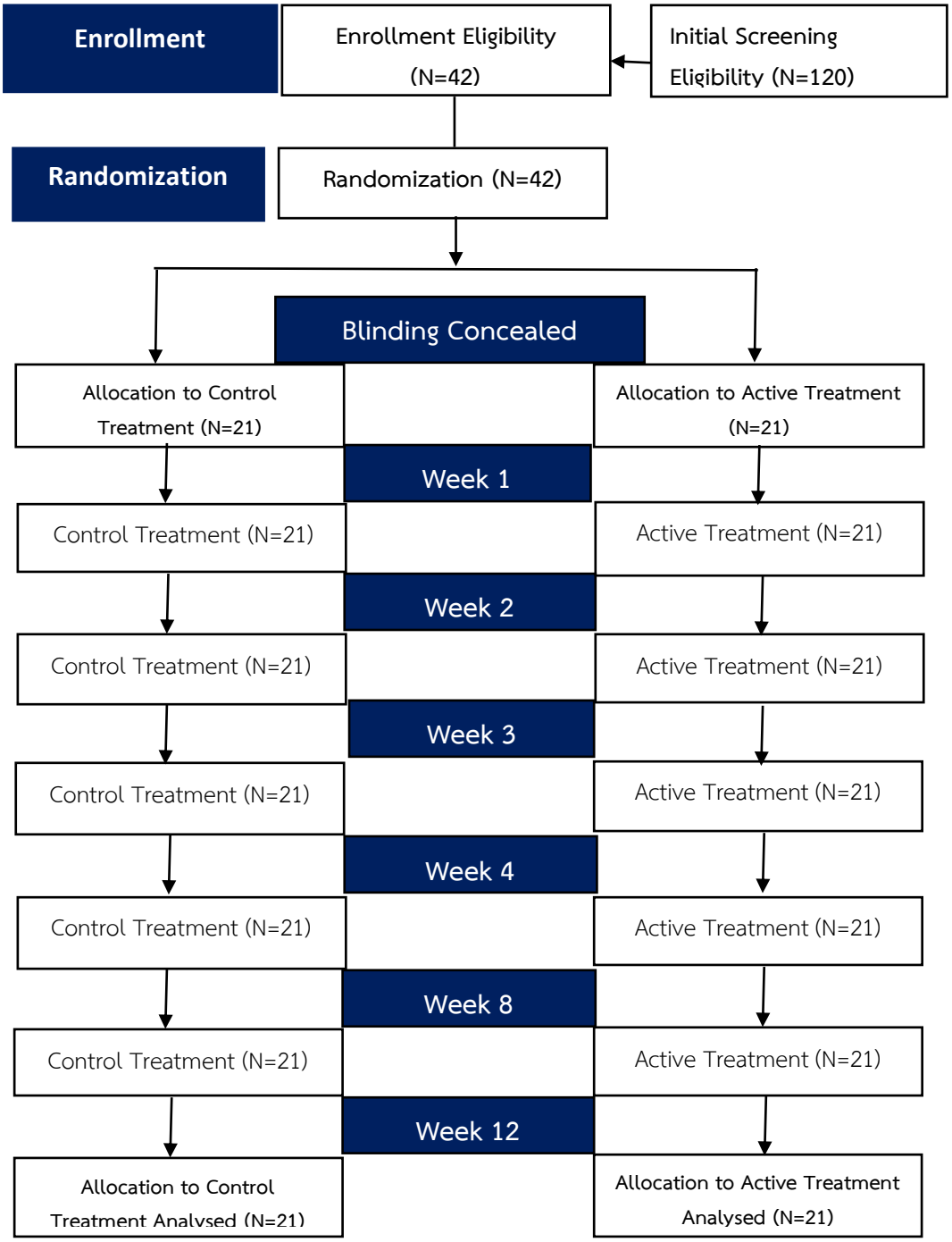
1. **Participant Flow:** A flow diagram showing participants involved at each stage.

**Patient Screening Flow-Chart**




**Note. 1.** Consecutive randomization **2.** Test products allocation were blinding b/w physician-nurse-patients **3.** Each of any one of two set of test products contained matching computerized allocated randomization numbers as series on products**.**

2. **Baseline Characteristics**: A summary showing baseline demographic (age and gender) and clinical characteristics of the participants.

**Table. 1** Demographic Characteristics

| Demographic | Control (N=21) Mean (SD), Min-Max, Range | Active(N=21) Mean(SD), Min-Max, Range | P-Value |
|---|---|---|---|
| Gender Female | 21 | 21 | |
| Age (in years) | 48.90 (6.09) 39-62, 23 | 47.00 (5.42) 39-58, 19 | 0.291 |
| Weight (in Kg) | 59.00 (6.05) 48-68, 20 | 60.81 (5.97) 49-74, 2 | 0.336 |
| Height (in CM) | 159.28 (6.93) 150-150, 2 | 160.23 (5.94) 149-170, 21 | 0.636 |
| Education Status | | | |
| Graduate | 4 (19.0%) | 7 (33.3%), | *0.157 |
| College | 5 (23.8%), | 11 (52.4%), | |
| Secondary | 12 (57.1%), | 3 (14.3%) | |
| Marital Status | | | |
| Single | 3 (14.3 %), | 11 (50.0 %), | |
| Married | 17 (80.9%) | 10 (45.2%) | *0.025 |
| Divorced | 1 (4.8%) | 1 (4.8%) | |

P-value by T-test, * P-value by Chi-Square Test

**Table. 2** Clinical Characteristics (A)

| Clinical Characteristics | Control (N=21)<br>Mean (SD),<br>Min-Max, Range | Active (N=21)<br>Mean (SD),<br>Min-Max, Range | P-Value |
|---|---|---|---|
| Gender Female | 21 | 21 | |
| Family History of CVI | Yes (0), No (21) | Yes (0), No (21) | - |
| Medical His-Comorbid | | | |
| None | 16 (76.2%), | 17 (80.1%), | |
| Hypertension | 5 (24.2%), | 2 (9.7 %), | *0.191 |
| Musculoskeletal | 0 (0%) | 2 (9.7%) | |
| Co-Medic (Self-Care) | | | |
| Sometime | 17 (82.5%), | 16 (77.8%), | *0.707 |
| Regular | 4 (17.5%) | 5 (22.3%) | |
| CEAP Classification | | | |
| CEAP C1 | 8 (38.0%), | 10 (47.6%) | *0.533 |
| CEAP C2 | 13 (62.0%) | 11 (52.4%) | |
| SBP (mmHg) | 138.95 (4.44)<br>129.0-146.0, 17.0 | 137.86 (4.06)<br>130.0-145.0,15.0 | 0.410 |
| DBP (mmHg) | 88.04 (3.90)<br>78.0-97.0, 19.0 | 88.57 (2.54)<br>83.0-92.0, 9.0 | 0.609 |
| Heart Rate (time per minute) | 70.81(4.08)<br>64.0-78.0, 14.0 | 70.33 (4.68)<br>60.0-78.0, 18.0 | 0.727 |
| Numbers of Leg Symptoms (symptom-Table 3) | 3.71(0.902)<br>3 - 6, 3 | 3.05(0.669)<br>2 - 4, 2 | *0.087 |

**P-value by T-test, * P-value by Chi-Square Test**

**Table. 3** Clinical Characteristics (B)

| Leg Symptoms | Control (N=21) Number (%), | Active (N=21) Number (%), | P-Value |
|---|---|---|---|
| Heavy Leg | | | |
| Yes | 7 (43.7%) | 9 (56.3%) | *0.525 |
| No | 14 (53.8%) | 12(46.2%) | |
| Leg Swelling | | | |
| Yes | 6 (56.7%) | 9 (43.3%) | *0.334 |
| No | 15 (40.0%) | 12 (60.0%) | |
| Leg Paiin | | | |
| Yes | 21 (50.0%) | 21 (50.0%) | - |
| No | 0 (0%) | 0 (0%) | |
| Night Cramp | | | |
| Yes | 12 (57.1%) | 7 (33.3%) | *0.121 |
| No | 9 (42.9%) | 14 (66.7%) | |
| Burning Sensation | | | |
| Yes | 0 (0%) | 0 (0%) | - |
| No | 21 (100%) | 21 (100%) | |
| Pin/Itching in Leg | | | |
| Yes | 1 (4.8%) | 0(0%) | *0.050 |
| No | 20 (95.2%) | 21(100.0%) | |
| Leg Itching | | | |
| Yes | 10(47.6%) | 4(19.1%) | *0.311 |
| No | 11(52.4%) | 17(80.9%) | |
| Varicose Vein | | | |
| Yes | 18 (85.7%) | 11 (52.4%) | *0.019 |
| No | 3 (14.3%) | 10 (47.6%) | |
| Spider Veins | | | |
| Yes | 3 (50.0%) | 3 (50.0%) | - |
| No | 18 (50.0%) | 18 (50.0%) | |

*** P-value by Chi-Square Test**

### 3. The Outcome Measures: Primary Outcomes-Responder Rate

**Table. 4** Venous Clinical Severity Score **(**VCSS**).** Responder **-**50 **%** Score Reduction **(**all patients**)**

| VCSS Total Score 50% Reduction | Control (N=21) Numbers with 50% Score reduction N/Total (%) | Active (N=21) Numbers with 50% Score reduction N/Total (%) | P-Value |
|---|---|---|---|
| After 4 weeks | 2/21 (9.52%) | 12/21 (57.14%) | *P=0.003 |
| After 8 weeks | 3/21 (14.28%) | 12/21 (57.14%) | *P=0.009 |
| After 12 weeks | 4/21 (19.04%) | 12/21 (57.14%) | *P=0.025 |

*P-value – Fisher's Exact

**Outcome Measures: Secondary Outcomes-Responder Rate Analysis by Attributes**

**Table. 5** Venous Clinical Severity Score **(**VCSS**).** Responder **-**50 **%** Score Reduction **(**Based on Severity CEAP Classification**)**

| **VCSS** Total Score **50%** Reduction | **Control** (N=**21**) Numbers with **50**% Score reduction **N/Total** (%) | **Active** (N=**21**) Numbers with **50**% Score reduction **N/Total** (%) | P-Value |
|---|---|---|---|
| **After 4 weeks** | | | |
| CEAP Class 1 | **0/8** (**0**%) | 6/10 **(**60.0**%)** | ***P=0.013** |
| CEAP Class 2 | **2/13** (**15.38** %) | 6/11 **(**54.54**%)** | ***P=0.082** |
| All CEAP Class 1**+**2 | **2/21** (**9.52**%) | 12/21 **(**57.14**%)** | ***P=0.003** |
| **After 8 weeks** | | | |
| CEAP Class 1 | 0/8 **(**9.52**%)** | 6/10 **(**60.0**%)** | ***P=013** |
| CEAP Class 2 | 3/13 **(**23.07**%)** | 6/11 **(**54.54**%)** | ***P=0.206** |
| All CEAP Class 1+2 | 3/21 **(**14.28**%)** | 12/21 **(**57.14**%)** | ***P=0.009** |
| **After 12 weeks** | | | |
| CEAP Class 1 | 0/8 **(**9.52**%)** | 6/10 **(**60.0**%)** | ***P=0.013** |
| CEAP Class 2 | 4/13 **(**30.76**%)** | 6/11 **(**54.54**%)** | ***P=0.408** |
| All CEAP Class 1+2 | 4/21 **(**19.04**%)** | 12/21 **(**57.14**%)** | ***P=0.025** |
| **All responder** | **4/21** (**19.04**%) | **12/21** (**57.14**%) | *P=0.025 |

***P-value – Fisher's Exact**

**Table. 6** Venous Clinical Severity Score **(**VCSS**).** Responder **-**50 **%** Score Reduction **(**Based on Presence of Co**-**morbidity**)**

| **VCSS** | **Control** (N=**21**) | **Active** (N=**21**) | |
|---|---|---|---|
| **Total Score 50%** | **Numbers with 50**% | **Numbers with 50**% | P-Value |
| **Reduction** | **Score reduction** | **Score reduction** | |
| | **N/Total** (%) | **N/Total** (%) | |
| **After 4 weeks** | | | |
| No Comorbidity | **1/16** (**6.25**%) | 9/17 **(**52.94**%)** | ***P=0.007** |
| With Comorbidity | **1/5** (**20.0** %) | 1/4 **(**25.0**%)** | ***P=0.206** |
| All Patients | **2/21** (**9.52**%) | 12/21 **(**57.14**%)** | ***P=0.003** |
| **After 8 weeks** | | | |
| No Comorbidity | 2/16 **(**12.50**%)** | 9/17 **(**52.94**%)** | ***P=026** |
| With Comorbidity | 1/5 **(**20.0**%)** | 3/4 **(**75.0**%)** | ***P=0.206** |
| All Patients | 3/21 **(**14.28**%)** | 12/21 **(**57.14**%)** | ***P=0.009** |
| **After 12 weeks** | | | |
| No Comorbidity | 3/16 **(**18.75**%)** | 9/17 **(**52.9**%)** | ***P=0.071** |
| With Comorbidity | 1/5**(**20.0**%)** | 3/4 **(**75.0**%)** | ***P=0.206** |
| All Patients | 4/21 **(**19.04**%)** | 12/21 **(**57.14**%)** | ***P=0.025** |
| **All responder** | 4/21 **(**19.04**%)** | 12/21 **(**57.14**%)** | ***P=0.025** |

***P-value-Fisher's Exact(Hyprtension7/42, Musculoskeletal Disorder2/42, No-comorbidity 33/42)**

**Disability assessed as Venous Clinical Severity Score (VCSS)-Total**

**Table. 7** Venous Clinical Severity Score **(**VCSS**). *** Total Score

| VCSS Total Sore | Control (N=21) Mean(SD), 95% CI, Min-Max | Active (N=21) Mean (SD), 95%CI Min-Max | *P-value |
|---|---|---|---|
| Day 0 | 27.2321 (6.4908), 24.2775 - 30.1850, 12.50-37.50 | 25.0000 (6.0917), 22.2271 - 27.7729, 15.63-34.38 | *0.257 |
| Week 4 | 22.4702 (7.9438), 18.8542 - 26.0862, 9.38-37.50 | 11.9048 (6.4908), 7.9673 - 15.8422, 0.00-31.25 | *<0.001 |
| Week 8 | 22.0238 (7.6849), 18.5257 - 25.5220, 9.38-37.50 | 17.1131 (8.3791), 8.3880 – 16.0168, 0.0-31.25 | *<0.001 |
| Week 12 | 21.7262 (7.4647), 18.3457 - 25.5220, 9.38-37.50 | 12.2024 (8.1432), 8.4956 - 15.9092, 0.0-31.25 | *<0.001 |

* P-value T-test (Active vs Controlled)

**Table. 8** Physician Rated Symptom Perception Score (PRSPS) Total Score

| PRSPS-<br>Total Score | Control (N=21)<br>Mean(SD), 95% CI, Min-Max | Active (N=21)<br>Mean (SD),95%CI, Min-Max | *P-<br>value |
|---|---|---|---|
| **Day 0** | 42.9630 (7.0038),<br>39.7749 - 46.1511, 33.33-57.78 | 37.1429 (6.8545),<br>34.0027 - 40.2630, 24. 44-51.11 | 0.010 |
| **Week 1** | 42.4339 (10.2222),<br>37.7555 - 47.1122, 26.67-60.00 | 30.8995 (9.4256),<br>26.6090 - 35.1900, 20.00-60.00 | <0.001 |
| **Week 2** | 39.7884 (9.8106),<br>35.3226 - 44.2541, 24.44-55.56 | 29.5238 (8.1994),<br>25.7915 - 33.2562, 20.00-53.33 | 0.001 |
| **Week 3** | 38.5185 (9.9711),<br>33.9797 - 43.0573, 22.22-53.33 | 27.3016 (8.4952),<br>23.4346 - 31.1686, 20.00-51.11 | <0.001 |
| **Week 4** | 38.4021 (9.9001),<br>31.8958 - 40.9086, 22.22-53.33 | 26.7725 (8.0294),<br>23.0356 - 30.5094, 20.00-46.67 | 0.001 |
| **Week 8** | 35.7672 (9.4256),<br>31.4767 - 40.0577, 22.22-51.11 | 26.1376 (8.4006),<br>22.3137 – 29.9615, 20.00-40.89 | 0.001 |
| **Week 12** | 35.8730 (10.7562),<br>30.9768 - 40.7692, 22.22-53.33 | 25.9259 (8.0226),<br>22.2741 - 29.5778, 20.00-48.89 | 0.002 |

*P-Value T-test (Active VS Controlled)

**Table. 9** Patient Self-Rated Symptom Score (PSSS). Total Score

| PSSS Total Score | Control (N=21) Mean(SD), 95% CI, Min-Max | Active (N=21) Mean (SD), 95% CI, Min-Max | *P-value |
|---|---|---|---|
| **Day 0** | 35.2585 (8.0086), 27.2499 - 43.2671, 30.86-50.57 | 31.7211 (6.2347), 25.4864 - 37.9558, 26.71-38.57 | P=0.118 |
| **Week 1** | 24.8980 (7.4151), 17.4831 - 32.4041, 26.71-38.57 | 19.2449 (5.0210), 14.2239 - 24.2659, 12.14-31.14 | P=0.006 |
| **Week 2** | 23.0680 (7.7269), 15.3411 - 30.7949, 26.86-37.29 | 17.1020 (4.8117), 12.2903 - 21.9137, 17.57-28.29 | P=0.005 |
| **Week 3** | 23.0816 (7.7273), 15.3543 - 30.8089, 26.86-37.14 | 16.9864 (5.0209), 23.4346 - 31.1686, 19.57-29.43 | P=0.004 |
| **Week 4** | 22.9524 (7.7321), 15.2203 - 30.6845, 26.86-36.86 | 16.8639 (4.9864), 11.9655 - 21.8503, 19.57-29.43 | P=0.004 |
| **Week 8** | 22.9592 (7.6331), 15.3261 - 30.5923, 27.57-36.86 | 16.7347 (4.7568), 11.9779 – 21.4915, 18.57-28.14 | P=0.003 |
| **Week 12** | 22.8571 (7.5951), 15.2620 - 30.4522, 25.86-35.86 | 16.6803 (4.6080), 12.0723 - 21.2883, 19.00-29.00 | P=0.003 |

*P-Value T-test (Active Vs Controlled)

**Table. 10** Medical Outcomes Study 12-Items Short-Form General Health Survey (MOS SF 12) – Physical Component Summary Score (PCS), Mental Component Summary Score (MCS) and Global Score (**Control Treatment– Baseline – the end of trial -Week 12**)

| **MOS –Item** | Control (N=21)-Day 0 | Control (N=21)- Week 12 | P-value |
|---|---|---|---|
| **SF 12** | Mean (SD), 95% CI, Min-Max | Mean (SD), 95% CI, Min-Max | |
| **PCS** | 84.6032 (3.06887), | 92.3810 (2.3904), | <.0.001 |
| | 76.67 – 90.00,13.33 | 86.67 – 93.33,6.67 | |
| **MCS** | 86.1905 (2.4234), | 86.3492 (2.5614), | 0.496 |
| | 76.67 -90.00,13.33 | 80 – 93.33,13.33 | |
| **Global** | 85.3965 (1.8184), | 89.3651(2.0052), | <0.001 |
| **Score** | 81.67 – 88.33,6.67 | 83.33 -93.33, 10.00 | |

**Table. 11** Medical Outcomes Study 12-Items Short-Form General Health Survey (MOS SF 12) – Physical Component Summary Score (PCS), Mental Component Summary Score (MCS) and Global Score

(**Active Treatment – Baseline - the end of trial- Week 12**)

| **MOS –Item** | Active (N=21)-Day 0 | Active (N=21)-Week 12 | P-value |
|---|---|---|---|
| **SF 12** | Mean (SD), 95% CI, Min-Max | Mean (SD), 95% CI, Min-Max | |
| **PCS** | 84.7619 (2.7021), | 92.5397 (1.7965), | <0.001 |
| | 80.00 -90.00,10.00 | 86.67 – 93.33,6.67 | |
| **MCS** | 86.8254 (0.7273), | 86.3492 (1.4547), | 0.245 |
| | 86.67 - 90.00,3.33 | 80 – 86.67,6.67 | |
| **Global** | 85.7937 (1.3559), | 89.4444 (1.0971), | <0.001 |
| **Score** | 83.33 -85.33, 5.00 | 86.67 -90.00, 3.33 | |

***P-value Paired T-Test**

**Table. 12** Medical Outcomes Study 14-Items Short-Form Chronic Venous Disease Survey (MOS CIVIQ 14) –Pain, Physical Function, Psychological-Social Function and Global Score (Control Treatment– the end of trial Week 12 - Baseline –Day 0)

| MOS CIVIQ 14 | Control (N=21)-Day 0 Mean (SD),Min-Max, Range | Control (N=21) Week 12 Mean (SD),Min-Max, Range | P-value |
|---|---|---|---|
| Pain | 61.4286(8.0843), 45.00 -75.00,30.00 | 67.8571 (7.6764), 60.00 – 75.00,15.00 | <0.001 |
| Physical Function | 58.7755(4.9597), 49.29 – 66.43,17.14 | 67.3469 (3.8075), 60.00 – 75.00,15.00 | <0.001 |
| Psycholo- & Social Function | 60.3571 (5.2013), 47.50 – 70.0022.50 | 68.6905 (4.3025), 60.00 – 75.00,15.00 | <0.001 |
| Global Score | 68.6905 (4.3025), 60.00 – 75.00,15.00 | 79.52 (5.5700), 68.57 – 91.43, | <0.001 |

*P-value Paired T-Test

**Table. 13** Medical Outcomes Study 14-Items Short-Form Chronic Venous Disease Survey (MOS CIVIQ 14) –Pain, Physical Function, Psychological-Social Function and Global Score (Active Treatment the end of trial -Week 12– Baseline – Day 0)

| MOS CIVIQ 14 | Active (N=21)-Day 0 Mean (SD), Min-Max, Range | Active (N=21)- Week 12 Mean (SD)I, Min-Max, Range | P-value |
|---|---|---|---|
| Pain | 63.5714 (9.3732), 45.00 – 75.00,30.00 | 70.7143 (6.9436), 60.00 -75.00,15.00 | <0.001 |
| Physical Function | 56.4286(5.4772), 49.29 -66.43, 17.14 | 66.9388 (3.0232), 64.29 -75.00, 10.71 | <0.001 |
| Psycholo- & Social Function | 61.3095 (5.7347), 52.50 -75.22, 5.00 | 70.4762 (2.6947), 65.00 -75.00, 10.00 | <0.001 |
| Global Score | 70.4762(2.6947), 65.00- 75.00,10.00 | 78.70 (5.8000), 76.06- 81.34 | <0.001 |

*P-value Paired T-Test

3. **Adverse Events:** A preliminary study on the Adverse Events report for both the Active and Controlled had been published in a separated publication and as such we presented only found as frequency tolerated by patients for the ends of trials.

https://www.tci-thaijo.org/index.php/EAUHJSci/article/view/101887

**Table. 14** Report of Adverse Event over 12-weeks period of follow-up.

| Summary Period | Control (N=21) Number, (%) | Active (N=21) Number, (%) | P-Value |
|---|---|---|---|
| Week 4 | No 7/21 (33.3 %), Some-Tolerate 14/21 (66.7%) | No 7/21 (33.3 %), Some-Tolerate 14/21 (66.7%) | 0.628 |
| Week 8 | No 12/21 (57.4 %), Some-Tolerate 9/21 (42.6 %) | No 14/21 (66.7 %), Some-Tolerate 7/21 (33.3%) | 0.376 |
| Week 12 | No 20/21 (95.1 %), Some-Tolerate 1/21 (4.9%) | No 18/21 (85.7 %), Some-Tolerate 4/21 (14.3%) | 0.756 |

**P-value Fisher's Exact Test**