Supplemental Material

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Table S1: Binary Study Outcomes by Treatment Group (Per-Protocol Analysis)

Outcome	PCDT n = 190		No PCDT n = 191		Risk Ratio		P Value
	Events	(%)	Events	(%)	Estimate	95% CI	
PTS: [1]							
Ulcer (any assessment)	9	(4.7%)	12	(6.3%)			
Villalta ≥ 5 (without ulcer)	82	(43%)	87	(46%)			
Late endovascular procedure only	1	(0.5%)	0	(0%)			
Total	92	(48%)	99	(52%)	0.92*	0.76, 1.12	0.43
PTS: VCSS ≥ 4 [1]	56	(29%)	78	(41%)	0.71*	0.54, 0.94	0.015
PTS incidence proportion: [2]							
At 6 months	48/165	(29%)	68/147	(46%)	0.63	0.47, 0.84	
At 12 months	56/152	(37%)	49/135	(36%)	1.02	0.75, 1.38	
At 18 months	42/135	(31%)	47/121	(39%)	0.80	0.57, 1.12	
At 24 months	46/142	(32%)	51/129	(40%)	0.82	0.60, 1.13	
Moderate-severe PTS: Villalta ≥ 10 [3]	35	(18%)	55	(29%)	0.63*	0.43, 0.91	0.013
Moderate-severe PTS incidence proportion: [4]							
At 6 months	19/165	(12%)	29/147	(20%)	0.58	0.34, 1.00	
At 12 months	18/152	(12%)	24/135	(18%)	0.67	0.38, 1.17	
At 18 months	16/135	(12%)	23/121	(19%)	0.62	0.35, 1.12	
At 24 months	16/142	(11%)	25/129	(19%)	0.58	0.33, 1.04	
Severe PTS: Villalta ≥ 15 [5]	17	(8.9%)	30	(16%)	0.56*	0.32, 1.00	0.044
Severe PTS: VCSS ≥ 8 [5]	13	(6.8%)	28	(15%)	0.45*	0.24, 0.87	0.013
Major non-PTS treatment failure	4	(2.1%)	4	(2.1%)	1.01	0.26, 3.96	0.99
Any treatment failures [6]	93	(49%)	102	(53%)	0.91*	0.75, 1.10	0.34
Major bleeding in first 10 days	3	(1.6%)	1	(0.5%)	2.02	0.37, 11.0	0.31
Any bleeding in first 10 days	7	(3.7%)	4	(2.1%)	1.39	0.63, 3.06	0.35
VTE:							
First 30 days	11	(5.8%)	4	(2.1%)	2.76	0.90, 8.53	0.064
Total over 24 months	26	(13.7%)	16	(8.4%)	1.63	0.91, 2.95	0.10
Death	6	(3.2%)	6	(3.1%)	1.01	0.33, 3.06	0.99

*Cochran-Mantel-Haenszel (CMH) test adjusted for center

[1] Cumulative proportion of patients who developed PTS (ulcer, Villalta ≥ 5 or LEP) at any time between 6 and 24 months inclusive; [2] At each visit, the proportion of patients with any PTS according to the Villalta scale among those who had an assessment performed (denominator); [3] Cumulative proportion with moderate or severe PTS (pre-specified analysis); [4] At each visit, the proportion of patients with any moderate or severe PTS according to the Villalta scale among those who had an assessment performed (denominator); [5] Cumulative proportion with severe PTS; [6] Composite of PTS or major non-PTS treatment failure. Villalta scores (0-33 range) – higher is worse; VCSS scores (0-27 range) – higher is worse.

PP, Per protocol analysis set; PTS, post-thrombotic syndrome; CI, confidence interval; VTE, venous thromboembolism

Table S2: Continuous Study Outcomes by Treatment Group (Per-Protocol Analysis)

Outcome	PCDT n = 196		No PCDT n = 195		PCDT – No PCDT Difference	
	n	**mean** (SE)	**n**	**mean** (SE)	**Estimate** (SE)	**P-value**
Villalta mean scores*: [(1)]						
At 6 months	165	3.72 (0.52)	147	5.39 (0.51)	-1.67 (0.48)	<0.001
At 12 months	152	3.78 (0.51)	135	5.47 (0.50)	-1.69 (0.46)	<0.001
At 18 months	135	3.84 (0.52)	121	5.56 (0.51)	-1.72 (0.49)	<0.001
At 24 months	142	3.90 (0.55)	129	5.64 (0.54)	-1.75 (0.55)	0.0016
VCSS mean scores†‡: [(2)]						
At 6 months	164	1.82 (0.33)	144	3.02 (0.32)	-1.20 (0.28)	<0.001
At 12 months	148	†	133	†	†	†
At 18 months	131	1.68 (0.35)	119	3.47 (0.35)	-1.79 (0.34)	<0.001
At 24 months	129	1.99 (0.35)	120	2.84 (0.36)	-0.85 (0.35)	0.015
SF-36 general Quality of Life‡: [(3)]						
PCS: Change, baseline to 24 months	138	10.51 (0.95)	126	11.45 (0.99)	-0.94 (1.18)	0.42
MCS: Change, baseline to 24 months	138	2.85 (0.82)	126	3.96 (0.87)	-1.11 (1.10)	0.31
VEINES disease-specific Quality of Life‡: [(4)]						
Overall: Change, baseline to 24 months	138	28.43 (1.98)	126	23.13 (2.08)	5.30 (2.57)	0.040
Symptoms: Change, baseline to 24 months	137	21.31 (1.98)	126	16.23 (2.08)	5.08 (2.58)	0.012
Leg pain severity§ (7-point scale)**: [(5)]**						
Change, baseline to Day 10	178	-1.79 (0.14)	173	-1.25 (0.14)	-0.54 (0.20)	0.0062
Change, baseline to Day 30	176	-2.39 (0.15)	168	-1.79 (0.15)	-0.61 (0.21)	0.0047
Index leg circumference§ (cm)**: [(6)]**						
Change, baseline to Day 10	172	-0.81 (0.23)	173	0.25 (0.23)	-1.06 (0.32)	0.0012
Change, baseline to Day 30	172	-1.39 (0.23)	167	-0.05 (0.23)	-1.35 (0.32)	<0.001

* Mean scores, standard errors (SE) and treatment differences estimated using growth curve models and piece-wise linear regression adjusted for center, and baseline covariates (age, sex, BMI, race)

† Model estimates are unchanged from month 6 to month 12 due to the lack of a significant time trend

‡ Mean scores, standard errors (SE) and treatment differences estimated using growth curve models and piece-wise linear regression adjusted for center, and baseline covariates (age, sex, BMI, race, Villalta score)

§ Mean change scores, SEs, and treatment differences estimated using multiple linear regression adjusted for center

(1) Villalta scores (0-33 range) – higher is worse; (2) VCSS scores (0-27 range) – higher is worse; (3) SF-36 major scales: physical component score (PCS, 0-100 range) and mental component score (MCS, 0-100 range) – higher is better, with a difference of 3 to 4 points considered clinically meaningful; (4) VEINES overall score (0-100 range) and symptom specific score (0-100 range) – higher is better; (5) patient-reported severity of pain in the index leg (0-7 range) – higher is worse; (6) leg circumference measured at 10cm below tibial tuberosity of the index leg.

Details of Growth Curve Modelling of the Villalta Scores

The repeated Villalta scores over time (i.e. at baseline, 1, 6, 12, 18, 24 months) were analyzed with growth curve mixed models using piecewise-linear regression.

The models take into account the correlation between the repeated observations, and they include both fixed effects: the pre-specified baseline factors (treatment, center, sex, and race), and continuous covariates (age at randomization, body mass index); and random effects (actual visit dates, patient). The full model includes all piece-wise time components, interaction terms (treatment x piece-wise time components), and the baseline factors.

Autoregressive and unstructured covariance matrix structures were tried to model the correlation between the repeated observations. Random effects are fit first, then the fixed effects. The best fitting model was determined by comparing Bayesian information criteria between candidate models. The least squares mean estimates were obtained from the best-fit model. All of the modelling was performed using SAS 9.4.