Supplementary Online Content

Hor CP, Fung WY, Ang HA, et al; Vitamin E in Neuroprotection Study (VENUS) Investigators. Efficacy of oral mixed tocotrienols in diabetic peripheral neuropathy: a randomized clinical trial. *JAMA Neurol.* Published online January 29, 2018. doi:10.1001/jamaneurol.2017.4609

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Symptoms and Scoring of TSS for DPN

Frequency/ Intensity	Absent	Mild	Moderate	Severe
Occasional	0	1·00	2·00	3·00
Often	0	1·33	2·33	3·33
Continuous	0	1·66	2·66	3·66

The symptoms were scored for paresthesia (pricking sensation), burning pain and lancinating pain, and asleep numbness.

eTable 2. Baseline Characteristics for Withdrawn Subjects by Study Group

Characteristics	Placebo	Tocotrienols	*p*-value
	n=32	n=39	
Male, %	40.6	41.0	0.973
Age, mean (SD), years	57.8 (10.23)	58.2 (9.93)	0.867
Duration of diabetes, mean (SD), years	9.8 (6.58)	11.7 (6.79)	0.260
Body mass index, mean (SD), (kg/m^2)	28.1 (6.29)	27.7 (5.38)	0.773
Treatment include insulin, %	50.0	53.8	0.747
Hypertension, %	68.8	74.4	0.601
Hypercholesterolemia, %	81.3	89.7	0.330
Ischemic heart disease, %	21.9	7.7	0.168
HbA_{1C}, %	9.3 (2.18)	9.2 (1.87)	0.890
Fasting blood glucose, mean (SD), mmol/L	9.3 (4.17)	8.5 (3.63)	0.390
Serum homocysteine, mean (SD), µmol/L	13.5 (4.42)	14.3 (9.51)	0.642
Serum vitamin B_9, mean (SD), ng/mL	8.8 (4.87)	10.0 (5.65)	0.328
Serum vitamin B_{12}, mean (SD), pg/mL	593.4 (224.07)	523.5 (37.62)	0.207
Total TSS, mean (SD)	6.5 (2.55)	7.8 (2.95)	0.061
Total NIS, mean (SD)	15.7 (8.33)	14.9 (9.76)	0.727

All values are presented as mean (SD) unless stated otherwise. HbA1c , glycated haemoglobin; TSS, Total Symptom Score; NIS, Neuropathy Impairment Score.

Seven subjects from placebo group and 12 from tocotrienols group withdrew due to adverse events. In the placebo group, 1 reported worsening of DPN symptoms, 2 with skin rashes, 1 non-specific soft tissue swelling of lower limb, 1 developed upper gastrointestinal bleeding, 1 had renal carcinoma and another underwent below knee amputation. In the tocotrienols group, 1 developed acute gastroenteritis, 1 skin rashes, 1 urinary tract infection with worsening of DPN symptoms, 1 non-specific soft tissue swelling, 1 neck pain, 1 bodyache, 1 headache, 1 minor epistaxis, 1 exacerbation of psoriasis, 1 acute flare of systemic lupus erythematosus, 1 varicose vein and 1 non-healing diabetic foot ulcer.

eTable 3. Total NIS and Component Score Changes Over 12 Months by Study Group

Component	**Placebo**		**Tocotrienols**		***p*-value (between groups)**
	Mean (SD)	*p*-value (within group)	Mean (SD)	*p*-value (within group)	
Total NIS					
Baseline (B)	15.8 (8.41)		16.2 (9.04)		
6-month (6M)	12.6 (7.82)	<0.001	14.9 (10)	0.010	
12-month (12M)	12.1 (8.67)	<0.001	13.4 (9.65)	<0.001	
Change (6M-B)	-3.3 (6.66)		-1.9 (7.89)		0.117
Change (12M-B)	-3.9 (7.47)		-3.3 (7.9)		0.529
Muscle strength (combined score for bilateral biceps, triceps, brachio-radialis, knee, ankle)					
Baseline (B)	0.2 (1.19)		0.1 (0.5)		
6-month (6M)	0.1 (0.57)	0.128	0.1 (0.61)	1.000	
12-month (12M)	0 (0)	0.135	0.2 (0.64)	0.574	
Change (6M-B)	-0.1 (0.86)		0 (0.43)		0.176
Change (12M-B)	-0.1 (0.98)		0 (0.67)		0.125
Reflex (combined score for bilateral biceps, triceps, brachio-radialis, knee, ankle)					
Baseline (B)	6.2 (5.65)		6.5 (6.28)		
6-month (6M)	4.7 (5.30)	<0.001	6.5 (6.50)	0.492	
12-month (12M)	5.1 (6.01)	0.026	5.8 (6.31)	0.110	
Change (6M-B)	-1.5 (4.6)		-0.3 (5.41)		0.073
Change (12M-B)	-1.1 (5.14)		-0.9 (5.83)		0.809
Sensation (combined score for bilateral index finger)					
Baseline (B)	3.3 (2.40)		2.9 (2.62)		
6-month (6M)	2.5 (2.52)	0.002	2.2 (2.48)	0.002	
12-month (12M)	1.9 (2.20)	<0.001	1.8 (2.22)	<0.001	
Change (6M-B)	-0.8 (2.75)		-0.9 (3.11)		0.698
Change (12M-B)	-1.3 (2.53)		-1.2 (3.18)		0.763
Sensation (combined score for bilateral great toe)					
Baseline (B)	6.2 (3.52)		6.8 (4.02)		
6-month (6M)	5.3 (3.52)	<0.001	6.1 (4.24)	0.01	
12-month (12M)	5.0 (3.41)	<0.001	5.6 (4.47)	<0.001	
Change (6M-B)	-1.0 (2.92)		-0.8 (3.39)		0.663
Change (12M-B)	-1.4 (3.19)		-1.3 (3.61)		0.853

NIS, Neuropathy Impairment Score.

eTable 4. Sensory Nerve Conduction Test by Study Group

Nerve / Sites		Baseline			Month-12	
	Placebo	Tocotrienols	*p*-value	Placebo	Tocotrienols	*p*-value
Median nerve						
Medial Palm- wrist						
Latency (ms)	2.5 (0.86)	2.5 (0.85)	0.931	2.4 (0.45)	2.5 (0.56)	0.521
Amplitude Pk-P (μV)	11.1 (4.82)	11.6 (6.63)	0.740	14.4 (9.7)	11.6 (5.55)	0.243
Velocity (m/s)	31.3 (5.32)	31 (5.66)	0.869	35.3 (5.97)	34.4 (7.34)	0.666
Ulnar Palm-wrist						
Latency (ms)	2.0 (0.33)	2.2 (0.91)	0.406	1.7 (0.24)	1.7 (0.18)	0.410
Amplitude Pk-P (μV)	8.8 (4.88)	9.7 (5.75)	0.533	8.8 (5.31)	8.4 (6.18)	0.825
Velocity (m/s)	41.3 (6.47)	40 (7.75)	0.524	50.5 (6.79)	48.3 (4.94)	0.255
Radial nerve						
Forearm- thumb						
Latency (ms)	2.0 (0.40)	2.0 (0.31)	0.932	2.1 (0.57)	2.2 (0.33)	0.547
Amplitude Pk-P (μV)	23.3 (11.59)	18.1 (13.69)	0.161	15.7 (9.07)	13.7 (8.68)	0.441
Velocity (m/s)	48.8 (5.8)	50.1 (7.52)	0.511	52 (9.31)	47.6 (6.17)	0.062
Sural nerve						
Calf- lateral malleolus						
Latency (ms)	2.5 (0.61)	3.2 (2.0)	0.166	2.3 (0.66)	2.5 (0.82)	0.463
Amplitude Pk-P (μV)	6.6 (8.65)	28.2 (91.22)	0.312	8.2(5.55)	6.7 (5.93)	0.415
Velocity (m/s)	45.4 (8.37)	42.6 (13.4)	0.438	48.4(10.13)	46.3 (9.99)	0.530

eTable 5. Glycemic Control Over 12 Months by Study Group

Biomarkers	**Placebo (n=150)**		**Tocotrienols (n=150)**		***p*-value (between groups)**
	Mean (SD)	*p*-value (within group)	Mean (SD)	*p*-value (within group)	
HbA_{1C}, %					
Baseline (B)	8.7 (1.82)		9.1 (1.97)		
6-month (6M)	8.9 (2.01)	0.034	9.3 (2.28)	0.412	
12-month (12M)	9.0 (2.17)	0.012	9.2 (2.08)	0.424	
Change (6M-B)	0.3 (1.47)		0.1 (1.69)		0.453
Change (12M-B)	0.4 (1.81)		0.1 (1.64)		0.190
Fasting blood glucose, mmol/L					
Baseline (B)	8.4 (3.34)		9.0 (4.24)		
6-month (6M)	8.8 (4.04)	0.049	9.0 (3.85)	0.917	
12-month (12M)	9.4 (4.75)	0.002	9.6 (5.18)	0.650	
Change (6M-B)	0.7 (3.81)		0 (4.86)		0.197
Change (12M-B)	1.3 (4.44)		0.3 (6.37)		0.172

HbA1c , glycated haemoglobin

eTable 6. Serum Homocysteine, Vitamins B_9 and B_{12} Over 12 Months by Baseline Homocysteine

Biomarkers	**Placebo**		**Tocotrienols**		***p*-value (between groups)**
	Mean (SD)	*p*-value (within group)	Mean (SD)	*p*-value (within group)	
Normohomocysteinemia, A-subgroup, <15μmol/L					
Homocysteine, μmol/L					
Baseline (B)	10.9 (2.28)		10.6 (2.39)		
6-month (6M)	11.5 (2.99)	0.019	11.2 (2.70)	0.019	
12-month (12M)	11.9 (3.55)	0.007	11.3 (3.18)	0.008	
Change (6M-B)	0.6 (2.33)		0.6 (2.23)		0.951
Change (12M-B)	1.0 (3.34)		0.8 (2.57)		0.717
Serum vitamin B_9, ng/mL					
Baseline (B)	10.1 (5.66)		9.8 (5.81)		
6-month (6M)	10.6 (6.18)	0.440	10.3 (5.15)	0.032	
12-month (12M)	10.4 (5.47)	0.752	9.8 (4.82)	0.487	
Change (6M-B)	0.4 (5.49)		1.1 (4.94)		0.395
Change (12M-B)	0.2 (5.66)		0.5 (5.92)		0.751
Serum vitamin B_{12}, pg/mL					
Baseline (B)	638.7 (335.53)		655.1 (328.70)		
6-month (6M)	594.7 (262.6)	0.032	682.3 (357.88)	0.918	
12-month (12M)	614.6 (312.02)	0.428	661.6 (315.13)	0.536	
Change (6M-B)	-47.1 (211.59)		-2.9 (249.41)		0.201
Change (12M-B)	-24.8 (292.05)		-24.0 (332.07)		0.987
Hyperhomocysteinemia, H-subgroup, ≥15μmol/L					
Homocysteine, μmol/L					
Baseline (B)	19.4 (5.60)		19.8 (8.39)		
6-month (6M)	13.9 (4.44)	<0.001	13.6 (3.51)	<0.001	
12-month (12M)	14.9 (6.21)	<0.001	14.4 (4.61)	<0.001	
Change (6M-B)	-5.9 (5.13)		-5.6 (4.70)		0.736
Change (12M-B)	-5.1 (5.80)		-4.9 (5.14)		0.852
Serum vitamin B_9, ng/mL					
Baseline (B)	7.5 (3.54)		8.0 (4.18)		
6-month (6M)	16.3 (8.53)	<0.001	14.6 (7.32)	<0.001	
12-month (12M)	14.7 (8.1)	<0.001	15.4 (7.55)	<0.001	
Change (6M-B)	8.8 (7.98)		6.6 (7.61)		0.225
Change (12M-B)	7.2 (8.51)		7.2 (8.08)		0.998
Serum vitamin B_{12}, pg/mL					
Baseline (B)	480.8 (177.99)		505.4 (267.53)		
6-month (6M)	703.9 (318.23)	<0.001	635.5 (315.82)	0.011	
12-month (12M)	663.6 (280.63)	<0.001	728.4 (404.09)	0.008	
Change (6M-B)	224.5 (303.12)		115.2 (274.46)		0.103
Change (12M-B)	183.4 (260.02)		193.8 (419.69)		0.905

eTable 7. Common Adverse Events Reported by Study Group

Event	Placebo		Tocotrienols		*p*-value (by events)
	Participants, n (%)	Events	Participants, n (%)	Events	
Adverse events	30 (20.0)	34	30 (20.0)	35	1
Cardiac disorders	0	0	1 (0.7)	1	1
Gastrointestinal disorders	1 (0.7)	1	3 (2.0)	3	0.622
Hepatobiliary disorders	0	0	1 (0.7)	1	1
Infections and infestations	8 (5.3)	8	3 (2.0)	3	0.218
Injury, poisoning and procedural complications	5 (3.3)	5	9 (6.0)	9	0.413
Metabolism and nutrition disorders	1 (0.7)	1	1 (0.7)	1	1
Musculoskeletal and connective tissue disorders	1 (0.7)	1	4 (2.7)	4	0.371
Nervous system disorders	4 (2.7)	4	1 (0.7)	1	0.371
Reproductive system and breast disorders	1 (0.7)	1	0	0	1
Respiratory, thoracic and mediastinal disorders	2 (0.7)	2	1 (0.7)	1	1
Skin and subcutaneous tissue disorders	10 (6.7)	10	9 (6.0)	9	1
Surgical and medical procedures	1 (0.7)	1	0	0	1
Vascular disorders	0	0	2 (1.3)	2	0.498

Some subjects developed more than one event throughout the study.

eTable 8. Serious Adverse Events Reported by Study Group

Event	Placebo		Tocotrienols		*p*-value (by events)
	Participants, n, (%)	Events	Participants, n, (%)	Events	
Serious adverse events	15 (10.0)	21	24 (16.0)	27	0.431
Cardiovascular disorders	6 (4.0)	9	3 (2.0)	3	0.138
Gastrointestinal disorders	2 (1.3)	2	0	0	0.498
Hepatobiliary disorders	0	0	1 (0.7)	1	1
Infections and infestations	1 (0.7)	2	10 (6.7)	10	0.035
Injury, poisoning and procedural complications	1 (0.7)	1	2 (1.3)	2	1
Metabolism and nutrition disorders	1 (0.7)	1	1 (0.7)	1	1
Psychiatric disorders	0	0	1 (0.7)	1	1
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.7)	1	1
Renal and urinary disorders	1 (0.7)	1	0	0	1
Skin and subcutaneous tissue disorders	2 (1.3)	2	3 (2.0)	3	1
Surgical and medical procedures	3 (2.0)	3	5 (3.3)	6	0.501

Some subjects developed more than one event throughout the study.