

Supplemental material for **Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: the multicentre, double-blind, randomised, sham-controlled PREMIUM trial** by Hans-Christoph Diener, MD, PhD; Peter J. Goadsby, MD, PhD; Messoud Ashina, MD, PhD; Mohammad Al-Mahdi Al-Karagholi, MD; Alexandra Sinclair, MD, PhD; Dimos Mitsikostas, MD, PhD; Delphine Magis, MD, PhD; Patricia Pozo-Rosich, MD, PhD; Pablo Irimia Sieira, MD, PhD; Miguel J.A. Lainez, MD, PhD; Charly Gaul, MD, PhD; Nicholas Silver, MBBS, PhD; Jan Hoffmann, MD, PhD; Juana Marin, MD; Eric Liebler; and Michel D. Ferrari, MD, PhD (on Behalf of the PREMIUM Study Group). *Cephalgia*.

Supplemental Table 1. Study inclusion and exclusion criteria

Inclusion Criteria

1. Between the ages of 18 and 75 years
2. Previous diagnosis of migraine (with or without aura) in accordance with the ICHD-III beta criteria
3. Experienced between 5 and 12 migraine days per month (over the course of the last 4 months) with at least 2 migraines lasting more than 4 hours
4. Age at migraine onset of less than 50 years
5. Agreed to refrain from using any migraine prevention treatments (including onabotulinumtoxinA injections) and/or medications (exclusive of medications taken for the acute relief of migraine symptoms)
6. Agreed to refrain from initiating or changing the type, dose, or frequency of any preventive medications for indications other than migraine that, in the opinion of the clinician, may have interfered with the study objectives (e.g. antidepressants, anticonvulsants, beta blockers)
7. Agreed to use the study device as intended, follow all requirements of the study including follow-up visits, and record required study data in the subject diary and other self-assessment questionnaires
8. Was able to provide written informed consent

Visit 2 Inclusion Criteria (Randomisation Visit)

1. Continued to meet all baseline (visit 1) eligibility criteria
 2. Had experienced 5 to 12 migraine days and fewer than 15 headache days during the
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4-week run-in period

Exclusion Criteria

1. Had a concomitant medical condition that would have required oral or injectable steroids during the study
 2. Had a history of any intracranial aneurysm, intracranial haemorrhage, brain tumour, or significant head trauma
 3. Had a structural abnormality at the site (e.g. lymphadenopathy, previous surgery, or abnormal anatomy)
 4. Had pain at the treatment site (e.g. dysaesthesia, neuralgia, and/or cervicalgia)
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5. Had another significant pain problem (e.g. cancer pain, fibromyalgia, or other head or facial disorder) that, in the opinion of the investigator, may have confounded the study assessments
 6. Had known or suspected severe cardiac disease (e.g. symptomatic coronary artery disease, prior myocardial infarction, CHF)
 7. Had known or suspected severe cerebrovascular disease (e.g. prior stroke or transient ischaemic attack, symptomatic carotid artery disease, prior carotid endarterectomy, or other vascular neck surgery)
 8. Had an abnormal baseline ECG (e.g. second- and third-degree heart block, prolonged QT interval, atrial fibrillation, atrial flutter, history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction)
 9. Had a previous cervical vagotomy
 10. Had uncontrolled high blood pressure (systolic >160 mm Hg or diastolic >100 mm Hg after 3 repeated measurements within 24 hours)
 11. Was implanted with an electrical and/or neurostimulator device (e.g. cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, cochlear implant, sphenopalatine ganglion stimulator, or occipital nerve stimulator)
 12. Had been implanted with metal cervical spine hardware or had a metallic implant near the stimulation site
 13. Had a known history of suspected secondary headache
 14. Had a history of syncope (within the last 5 years)
 15. Had a history of seizures (within the last 5 years)

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16. Had a known or suspected substance abuse disorder or addiction (within the last 5 years)
 17. Was using marijuana (including medical marijuana) for any indication more than twice a month
 18. Was taking simple analgesics or NSAIDs for more than 15 days per month or was taking triptans, ergots, or combined analgesics for more than 10 days per month for headaches or other body pain
 19. Was taking opioids for more than 2 days per month for headaches or body pain
 20. Had taken medications for migraine prevention in the previous 30 days
 21. Had a previous diagnosis of medication overuse headache that had reverted to episodic migraine within the last 6 months
 22. Met the ICHD-III beta criteria for chronic migraine (>15 headache days per month)
 23. Had failed an adequate trial (2 months or longer) of at least 3 classes of a drug therapy for the prevention of migraine
 24. Had previous surgery for migraine prevention
 25. Had undergone nerve block (occipital or other) in the head or neck within the last 2 months
 26. Had received onabotulinumtoxinA injections within the last 6 months
 27. Was pregnant or thinking of becoming pregnant during the study period or was of childbearing years and unwilling to use an accepted form of birth control
 28. Was participating in any other therapeutic clinical investigation or had participated in a clinical trial in the preceding 30 days

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29. Belonged to a vulnerable population or had any condition that would compromise his or her ability to provide informed consent, comply with the follow-up requirements, or provide self-assessments (e.g. homeless, developmentally disabled, prisoner)
 30. Was a relative or an employee of the investigator or clinical study site
 31. Had a psychiatric or cognitive disorder and/or behavioural problems that, in the opinion of the clinician, may have interfered with the study
 32. Had previously used the study device

Visit 2 Exclusion Criteria (Randomisation Visit)

1. Had initiated or changed the type, dose, or frequency of any preventive medication for indications other than migraine that, in the opinion of the clinician, may have interfered with the study objectives during the 4-week run-in period

CHF: congestive heart failure; ECG: electrocardiogram; ICHD-III beta: International Classification of Headache Disorders, 3rd edition (beta version); NSAID, non-steroidal anti-inflammatory drug.

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Supplemental Table 2. Adherence with treatment

Adherence	nVNS^a	Sham^a
Month 1 ≥67%	151 (92.1)	155 (92.8)
(Days 1-28) ^b <67%	13 (7.9)	12 (7.2)
Month 2 ≥67%	141 (91.0)	142 (91.6)
(Days 29-56) ^b <67%	14 (9.0)	13 (8.4)
Month 3 ≥67%	128 (88.3)	129 (91.5)
(Days 57-84) ^b <67%	17 (11.7)	12 (8.5)

^a Data are n (%) among patients from the ITT population who had available adherence data; percentages are determined for each patient for each 4-week period as 100 × actual administrations/expected administrations.

^b Month 1: nVNS, n=164; sham, n=167. Month 2: nVNS, n=155; sham, n=155.

Month 3: nVNS, n=145; sham, n=141.

ITT: intent-to-treat; nVNS: non-invasive vagus nerve stimulation.

Supplemental Table 3. Demographics and patient characteristics (mITT population)

Characteristic^a	nVNS (n=138)	Sham (n=140)
Age, y	43.9 ± 11.0	41.8 ± 12.0
Age at migraine onset, y	19.7 ± 9.6	20.1 ± 10.1
Female, n (%)	119 (86.2)	115 (82.1)
Caucasian, n (%)	135 (97.8)	128 (91.4)
Migraine type, n (%)		
Migraine with aura ^b	34 (24.6)	37 (26.4)
Migraine without aura ^b	104 (75.4)	103 (73.6)
Migraine days in the last 4 weeks, n	8.1 ± 2.1	8.1 ± 2.1
Headache days in the last 4 weeks, n	8.9 ± 2.6	9.0 ± 2.6
Acute migraine medication use per month, d	7.0 ± 2.6	7.1 ± 3.0

^a Data are mean ± SD unless otherwise indicated. ^b Presence/absence of aura was based on diagnosis provided in subject medical history at enrolment.

mITT: modified intent-to-treat; nVNS: non-invasive vagus nerve stimulation; SD: standard deviation.