Transcutaneous auricular vagus nerve stimulation versus sham stimulation in patients with erosive hand osteoarthritis (ESTIVAL): a randomised, multicentre, double-blind, sham-controlled trial

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Summary

Background Erosive hand osteoarthritis is a painful and inflammatory disease without effective treatments. In this study we aimed to investigate the efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) compared with sham stimulation in patients with inflammatory erosive hand osteoarthritis.

Methods ESTIVAL was a multicentre, randomised, double-blind, sham-controlled trial done in 18 French hospital centres (two secondary and 16 tertiary centres). Adults (aged ≥18 years), fulfilling the American College of Rheumatology criteria for hand osteoarthritis with at least one erosive interphalangeal joint and ultrasound-confirmed synovitis were randomly assigned (1:1), stratified by site, using centralised web-based randomisation with computer-generated allocation, to receive either daily 20-min taVNS (VAGUSTIM, Schwa Medico, Rouffach, France) or sham stimulation (sham group; no electrical current) for 12 weeks. The primary endpoint was change in hand pain on a visual analogue scale (VAS) from baseline to week 12. Safety was assessed by recording adverse events and serious adverse events at each visit using a standardised form completed by investigators. The primary outcome and safety were analysed in the intention-to-treat population. The trial was registered with ClinicalTrials.gov, NCT04520516, and is completed. No individuals with lived experience of hand osteoarthritis were involved in the design or conduct of the study.

Findings Between April 8, 2021, and March 29, 2022, 148 patients were enrolled in the study and 142 (96%) were randomly assigned (73 [51%] to the taVNS group and 69 [49%] to the sham group). Overall, the mean age was 66·5 years (SD 8·4), 125 (88%) of 142 participants were female, and 17 (12%) were male. At week 12, 63 (86%) of 73 participants in the taVNS group and 64 (93%) of 69 participants in the sham group provided primary outcome data. Median change in VAS hand pain was –16·0 mm (IQR –32·0 to 5·0) in the taVNS group versus –6·0 mm (–27·0 to 7·0) in the sham group, giving an adjusted between-group difference of –10·0 mm (95% CI –23·0 to 2·0; p=0·22) at week 12; the primary endpoint was not met. No serious adverse events occurred. Adverse events were reported by 22 (30%) of 73 participants in the taVNS and 16 (23%) and 69 participants in the sham group, with no emerging safety concerns.

Interpretation In participants with erosive hand osteoarthritis, taVNS was safe and well tolerated. Although the primary endpoint was not met, the consistent pain reduction observed in patients with greater synovial inflammation suggests that taVNS merits further investigation in this erosive hand osteoarthritis population.

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Introduction

Symptomatic hand osteoarthritis affects 8–16% of individuals older than 50 years.[1] Hand osteoarthritis is a disabling condition which impacts daily life activities including writing, eating, dressing, or lifting objects.[2] Hand osteoarthritis is a heterogeneous disorder encompassing various clinical phenotypes and erosive hand osteoarthritis has emerged as the most severe phenotype within the spectrum of hand osteoarthritis. It affects the interphalangeal joints and is defined by the presence of radiographic central erosion, according to the Verbruggen score.[3] Erosive hand osteoarthritis represents approximately 10% of symptomatic hand osteoarthritis, with a substantially higher prevalence ranging from 40% to 50% observed in specialised tertiary care settings.[4,5] It is distinguished by chronic synovitis, progressive destruction of the interphalangeal joints, persistent pain, and considerable disability.[4] Despite the

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Research in context

Evidence before this study

Hand osteoarthritis is a common, painful and disabling condition. Among individuals with symptomatic hand osteoarthritis, 10% have a more severe subtype called erosive hand osteoarthritis, defined by radiographic central erosion. Erosive hand osteoarthritis is associated with increased hand pain, number of joints with synovitis, systemic low-grade inflammation, and disability. Despite its prevalence, specific treatment of erosive hand osteoarthritis has not been established. Therapeutic options are scarce and might be ineffective or have substantial side-effects in this older (aged >50 years) population. Vagus nerve stimulation has been known for decades to decrease inflammation through the anti-inflammatory cholinergic pathway. An efficient transcutaneous device that can activate the afferent branch of the vagus nerve at the cymba concha has been developed and appears to be safe. We searched PubMed with no language restrictions for articles published from database inception to Feb 22, 2025, using the search terms "vagus nerve" and "hand osteoarthritis". We found no randomised controlled trials. In an open-label study in 18 patients with erosive hand osteoarthritis, vagus nerve stimulation ameliorated hand pain and function. Therefore, we hypothesised that transcutaneous auricular vagus nerve stimulation could ameliorate pain and function in inflammatory erosive hand osteoarthritis compared with sham stimulation.

Added value of this study

To our knowledge, this is the first randomised controlled study to investigate the effect of transcutaneous auricular vagus nerve stimulation in erosive hand osteoarthritis with inflammatory features. Although the primary endpoint was not met, the study suggests that transcutaneous auricular vagus nerve stimulation might provide clinical benefit in a subgroup of patients with signs of local inflammation, particularly in terms of pain relief. The study also confirms the feasibility and excellent tolerability of neuromodulation in this older population, supporting the exploration of neuroimmune pathways in the treatment of osteoarthritis.

Implications of all the available evidence

This first proof-of-concept randomised study provides a rationale to conduct further randomised controlled trials of transcutaneous auricular vagus nerve stimulation in patients with erosive hand osteoarthritis and a high level of inflammation.

disease's prevalence, existing pharmacological treatments for hand osteoarthritis and erosive hand osteoarthritis have minimal effectiveness in managing pain. Efficacy of paracetamol versus placebo has yet to be assessed in hand osteoarthritis but has shown significant but non-clinically meaningful results in knee osteoarthritis, although there are safety concerns surrounding non-steroidal anti-inflammatory drug (NSAID) use in this older and comorbid population.[2] While glucocorticoids and methotrexate have shown the potential for symptom relief in inflammatory hand osteoarthritis, questions remain about their long-term safety, and they have not specifically been studied in erosive hand osteoarthritis.[6,7] Studies exploring other immunomodulatory agents (ie, hydroxychloroquine, TNF, IL-6, or IL-1 inhibitors and anti-bone resorptive drugs such as denosumab) in hand osteoarthritis have not shown significant pain relief, while denosumab showed a reduction in the development of new erosive joints.[2,8] The pathogenesis of erosive hand osteoarthritis is influenced substantially by systemic and joint inflammation, but a gap still remains in our understanding of this disease. Therefore, there is an urgent need for innovative and safe therapeutic approaches, to effectively address the challenges of treating erosive hand osteoarthritis.

The vagus nerve, beyond its autonomic functions in regulating heart rate and gastrointestinal activity, plays a critical role in modulating inflammation.[9,10] Vagus nerve stimulation activates the cholinergic anti-inflammatory pathway, whereby afferent branches of the vagus nerve detect peripheral inflammation, and their efferent branches suppress the production of pro-inflammatory cytokines in splenic macrophages through acetylcholine binding to the α7 acetylcholine nicotinic receptor (α7nAchR).[9] While invasive surgical techniques are used for vagus nerve stimulation in epilepsy or depression and have been studied in rheumatoid arthritis, transcutaneous auricular vagus nerve stimulation (taVNS) offers a non-invasive alternative by targeting the auricular branch of the vagus nerve at the cymba conchae.[11–13] We previously did an open-label, pilot, uncontrolled study (ADEPT)[14] to assess taVNS in 18 patients with symptomatic inflammatory erosive hand osteoarthritis. Following 4 weeks of taVNS treatment, we observed a reduction in pain and improvement in function and, importantly, no serious adverse events occurred.[14]

On the basis of these preliminary data, we hypothesised that taVNS would lead to decreased pain and improved function at 12 weeks compared with sham stimulation in patients with erosive hand osteoarthritis, with a good safety profile.

Methods

Study design and participants

The ESTIVAL (*Essai randomisé comparant stimulation auriculaire transcutanée du nerf vague versus sham stimulation dans l'arthrose digitale érosive symptomatique et inflammatoire*) trial was a parallel, multicentre, randomised, double-blind, sham-controlled study done

in 18 French hospital centres (two secondary and 16 tertiary centres; appendix p 2).

Patients with erosive hand osteoarthritis and synovitis were referred from other hospitals, private rheumatology offices, and the community, including patient associations and general media. We included adults (aged ≥18 years), with hand osteoarthritis according to the American College of Rheumatology criteria with hand pain intensity of at least 40 mm on a 0–100 mm visual analogue scale (VAS) on at least half of the days over the past 30 days; an inadequate response, adverse effects, or contraindications to existing medications (including paracetamol, topical, and oral NSAIDs); presence of at least one symptomatic interphalangeal joint with clinical synovitis defined by soft tissue swelling on palpation; and presence of at least one radiographic erosive interphalangeal joint according to the phase E or R of the Verbruggen–Veys score.[3] Main exclusion criteria were predominant or isolated thumb base osteoarthritis; other rheumatic diseases; history of local cutaneous disease affecting the left ear; symptomatic orthostatic hypotension; or a history of repeated vasovagal syncope, prior vagotomy, or pregnancy; and known history of cardiac rhythm disturbances or atrioventricular block indicated on electrocardiogram (ECG; full list of exclusion criteria in appendix p 3). Following inclusion, participants underwent hand ultrasound and electrocardiogram assessments. Participants with at least one interphalangeal joint showing ultrasound synovitis (defined by a grey-scale synovitis score of 2 or 3 or power Doppler signal score ≥1, or both), without ECG contraindication and negative urinary β-hCG if appropriate, were eligible for randomisation. Ethnicity was not recorded, in accordance with French regulations on data collection. Sex was self-reported, with only binary options available (male or female). All participants provided informed written consent and were required to be affiliated with a social security scheme. The study was in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee for the Protection of Individuals Ile de France V (Ile de France-no 2020-A02213_36). The protocol followed CONSORT guidelines[15] and is published elsewhere.[16] The trial was registered with ClinicalTrials.gov, NCT04520516, and is completed. No individuals with lived experience of hand osteoarthritis were involved in the design or conduct of the study.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either taVNS or sham stimulation using a secure web-based response system available in each study centre (CleanWEB e-CRF, Telemedicine Technologies, Boulogne-Billancourt, France). Randomisation was stratified by centre. The block randomisation list was established by an independent biostatistician, not involved in participant recruitment, using computer-generated random numbers and varying block sizes (blocks of size 2 or 4). Investigators had no access to the randomisation list and were masked to the size of blocks. Manufacturing and preparation of the medical devices were managed by Schwa-Medico and anonymised by the General Agency for Health Equipment and Products, after which devices were delivered to the clinical pharmacy at each participating site. Each device was associated with an identifying number that linked the device to its assigned treatment type (active stimulation or sham). Both active and sham devices were identical in appearance. To ensure consistency in patient education regarding device usage across centres and masking, a standardised document containing explanations was prepared by the study coordinator and provided to a clinical nurse at each site. Education sessions were provided by investigators independent from those performing outcome assessments. During follow-up, clinical efficacy was assessed before safety and side-effects. Patients, outcome assessors, and data analysts were masked to treatment allocation.

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See Online for appendix

Procedures

taVNS was performed using the VAGUSTIM device from Schwa Medico, Rouffach, France, CE-marked medical device (CE0197; certificate issued April 28, 2020). At baseline, the participant applied the electrode (Monath Electronic Medico, Rouffach, France) under the supervision of the investigator, nurse, or clinical research technician, ensuring its appropriate use. A conductive gel (C+V Pharma Depot, Versmold, Germany) was used to attach the electrode to the cymba concha of the left ear, as the left vagus nerve does not innervate the cardiac sinus node. This stimulation was administered daily for 20 min over a 12-week period. Stimulation parameters included a frequency of 25 Hz and a pulse duration of 100 μs. The intensity of stimulation was gradually increased from 0 mA up to 8 mA, or until the patient experienced discomfort, with daily adjustment to ensure a comfortable and tolerable experience. In the sham group, participants used an identical device and were instructed to increase the intensity in the same manner (up to 8 mA or discomfort threshold), but no electrical signal was delivered. Paracetamol was allowed as a rescue pain medication, except within the 48 h before each study visit, and NSAIDs were not permitted at all during the study.

Participants were followed up at weeks 4, 8, and 12, during which clinical assessments, patient questionnaires, adverse event monitoring, and device adherence tracking were conducted. Baseline and week-12 blood samples were collected to assess changes in inflammatory (high-sensitivity C-reactive protein [hs-CRP], IL-6, IL-8, and TNF) and catabolic markers (type II collagen [coll 2]-1 concentration and coll2-1-nitrated [coll2-1 NO_2]) by immunoassays. Antero-posterior hand radiographs were recorded at baseline and assessed using the Kellgren–Lawrence system and the Verbruggen–Veys phase score (0–32, all proximal and distal interphalangeal, trapezio-metacarpal, scaphotrapeziotrapezoid) by one single trained reader (EM).[3,17] A baseline hand ultrasound of

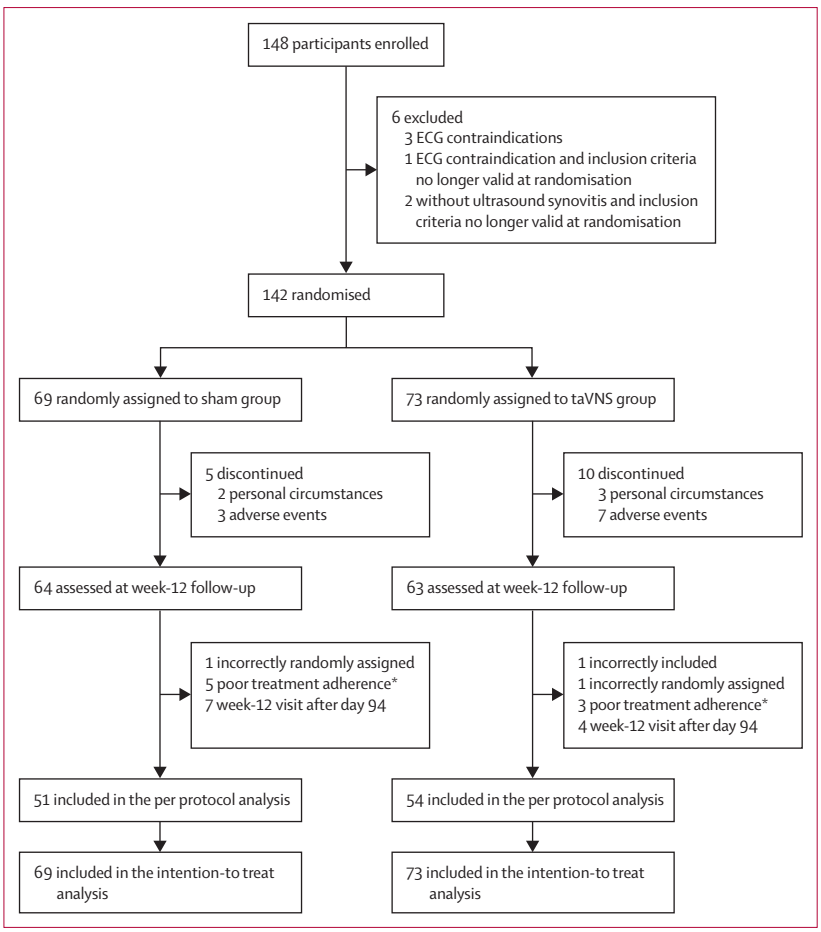

Figure 1: **Trial profile**
ECG=electrocardiogram. taVNS=transcutaneous auricular vagus nerve stimulation. *Less than 80% of days of medical device use.

interphalangeal joints was done to assess inclusion criteria. Additionally, a subset of patients from Saint-Antoine Hospital underwent non-contrast enhanced hand MRI at baseline and week 12 using whole-body 1·5 Tesla or 3·0 Tesla MRI machines. One trained reader (LM) analysed the baseline and 12-week MRIs with known time sequences for each treatment period while remaining masked to treatment allocation. Synovitis and bone marrow lesions were scored using a modified Outcome Measures in Rheumatology/Hand Osteoarthritis MRI Scoring System (OMERACT/HOAMRIS) score on proximal and distal interphalangeal of the 2nd to 5th finger.[18]

Outcomes

The primary endpoint was the between-group difference of the variation of self-reported hand pain measured on a 0–100 mm VAS from baseline (week 0) to week 12 (week 12 minus week 0 VAS value). Patients responded to the standard question recommended by the Osteoarthritis Research Society International (OARSI): "How much pain in your hands did you experience during the past 48 hours?"[19]

Secondary outcomes were score differences from week 0 to week 12 (week 12 minus week 0 value) on the Australian–Canadian Osteoarthritis (AUSCAN) pain, function, and stiffness scales (normalised 0–100, 100 indicating the worst possible score); modified Functional Index for Hand Osteoarthritis (FIHOA) scale score (0–100, 100 indicating the worst possible score); Cochin hand functional disability scale score; EQ-D5 score; Hospital Anxiety and Depression (HAD) scale score; fatigue intensity (0–100 mm VAS); number of painful and swollen hand joints (0–30); patient global assessment score on a 0–100 mm (100 being the best) VAS; and the Douleur Neuropathie-4 score (DN-4) questionnaire assessing the neuropathic pain component. Additionally, we assessed the total consumption of paracetamol (in grams) over 12 weeks. We assessed the proportion of patients reaching the patient acceptable symptom state for pain score (0–100), defined as a VAS hand pain score below 40 out of 100, OMERACT-OARSI responders, and patient global impression of change scores (0 for no change or worse to 7 for considerable improvement, with scores of 5–7 considered responders) at week 12. Biological endpoints included changes in inflammatory markers (hs-CRP [mg/L], IL-6 [pg/mL], IL-8 [pg/mL], and TNF [pg/mL]) and serum biomarkers of cartilage degradation (coll2-1 and its nitrated form coll2-1 NO_2). MRI synovitis and bone marrow lesions at week 12 were also assessed. Safety endpoints were the proportion of adverse events. Compliance endpoints involved the mean daily use and cumulative use time of the VAGUSTIM device collected from the device's tracker over the past 30 days before each visit.

Pre-specified exploratory endpoints consisted of the hip or knee Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (0–20) only in patients with knee or hip pain, the ease of device use (on a 4-point scale from very easy to very difficult), the proportion of patients believing they were in the active treatment group, and treatment satisfaction at week 12 (on 5-point scale from very satisfied to not at all satisfied). We did a pre-specified sensitivity analysis of the primary endpoint (difference between week 12 and week 0 in hand pain on VAS) and the OMERACT responders, which was based on the number of joints with clinical or ultrasound synovitis at baseline (patients were divided into two groups: ≥2 joints with synovitis or <2 joints with synovitis for first analysis and ≥median number of synovitis or <median for the second analysis), the level of disability (using FIHOA in tertile groups), and the presence of neuropathic pain (defined as DN4 score ≥3 and ≥4).

Statistical analysis

To detect a difference between groups of at least 13·0 mm change on VAS pain at 12 weeks, considering a mean improvement in the sham group of 11·3 mm (SD 24·0),[20] a two-sided α of 0·05, 80% power using a Wilcoxon–Mann–Whitney test, and a 20% drop-out rate, 142 randomly assigned patients were needed.

Considering the frequency of ultrasonographic features of joint inflammation of interphalangeal joints in erosive hand osteoarthritis, we planned to include 171 patients (20% more) to randomly assign 142. The primary analysis was done in the intention-to-treat population, defined as all patients randomly assigned.

The per-protocol population included all randomly assigned participants with an available primary endpoint and without major protocol deviations (ie, wrongly included or randomly assigned, poor compliance with less than 80% of the planned number of days using the device, or a week-12 visit done more than 15 days late). The safety population included all randomly assigned participants who underwent at least one training session for the use of the device with the nurse.

Baseline characteristics of patients were described using mean (SD) or median (IQR) for continuous variables, depending on the distribution and using frequency and percentage for qualitative variables.

In the intention-to-treat analysis, the primary outcome was compared between groups (taVNS group minus sham group) using a Wilcoxon rank-sum test and median difference with its 95% CI using the bootstrap method (with 1000 resamples). VAS pain change at week 12 being normally distributed, the mean (SD) of each group and mean difference between groups (taVNS group minus sham group) with its 95% CI using normal approximation method were also provided. For patients with missing outcome data at week 12, we did single imputation, and missing VAS values at week 12 were replaced by the mean group VAS value at week 0. Sensitivity analyses were done in the intention-to-treat population with available data, on the per protocol population, and using a linear mixed model adjusted on week 0 VAS pain score and considering each participating centre as a random effect.

For secondary and exploratory outcomes, we did complete case analyses (missing data were not replaced). Secondary outcomes were compared between groups using χ^2 test with Yates' continuity correction for qualitative outcomes and Student *t* test or Wilcoxon rank-sum test for quantitative outcomes, according to their distribution. For secondary and exploratory outcomes, treatment effect was expressed using the between-group difference (taVNS group minus sham group) with its 95% CI estimated using a normal approximation for means, bootstrap method (with 1000 resamples) for medians, and Clopper–Pearson exact method for percentages. Given the small number of patients for whom the HOAMRIS sub-score joints with synovitis and bone marrow lesions) changes at week 12 were available, only individual values were reported, and no comparison between groups was made. We did between-group comparisons of the total number of days of use over the 12-week period, mean daily use duration over the 12 weeks, and mean intensity use over the 12 weeks. Furthermore, we calculated Spearman correlations coefficients between baseline concentrations of biomarkers and primary endpoint (VAS hand pain between week 0 and week 12) in the taVNS group.

The statistical analysis was done using SAS (version 9.4) and R (version 4.1.2). All tests were two-sided and a p value of less than 0·05 indicated statistical significance.

	Sham group (n=69)	taVNS group (n=73)
Age, years	66·7 (9·1)	66·3 (7·9)
Sex		
Male	7 (10%)	10 (14%)
Female	62 (90%)	63 (86%)
BMI, kg/m²	25·6 (5·3)	24·2 (4·4)
Cardiac frequency, beats per minute*	71·7 (16·5)	67·9 (10·1)
Systolic blood pressure, mm Hg	133·5 (15·1)	131·1 (16·9)
Diastolic blood pressure, mm Hg	74·8 (10·4)	73·5 (10·3)
Hand ultrasound synovitis, number of joints	5·0 (3·0–9·0)	5·0 (3·0–8·0)
Hand Kellgren—Lawrence total score, 0–128	45·3 (17·9)	43·4 (16·6)
Number of hand erosive joints (E or R), 0–32†	4·0 (2·0–7·0)	4·0 (2·0–7·0)
Erosive E joints†	2·0 (1·0–2·0)	2·0 (1·0–4·0)
Erosive R joints†	2·0 (0·0–4·0)	1·0 (0·0–4·0)
Number of joints with MRI synovitis (OMERACT/HOAMRIS), 0–8‡§	5·0 (2·2)	4·8 (2·4)
Number of MRI bone marrow lesions (OMERACT/HOAMRIS), 0–8‡§	3·1 (2·1)	4·7 (3·3)
Paracetamol consumption in the past 7 days	26 (38%)	33 (45%)
Total consumption of paracetamol over the past 7 days in consumers, g	2·5 (1·0–7·0)	2·0 (1·0–4·0)
Symptomatic knee osteoarthritis	27 (39%)	33 (45%)
Symptomatic hip osteoarthritis	8 (12%)	10 (14%)

Data are n (%), median (IQR), or mean (SD). E=erosive. HOAMRIS=Hand Osteoarthritis MRI Scoring system. OMERACT=Outcome Measures in Rheumatology. R=remodelling. taVNS=transcutaneous auricular vagus nerve stimulation. *Three missing values in the taVNS group. †Four missing values in the sham group and five missing values in the taVNS group. ‡Seven participants with available data in the sham group and six in the taVNS group. §Assessment of the interphalangeal joints of the 2nd to 5th raw in seven patients in the sham group and six patients in the taVNS group.

Table 1: **Baseline characteristics**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 8, 2021, and March 29, 2022, we enrolled 148 patients, 142 (96%) of whom were randomly assigned (73 [51%] to the taVNS group and 69 [49%] to the sham group) and included in the intention-to-treat analysis (figure 1). 63 (86%) of 73 in the taVNS group and 64 (93%) of 69 in the sham stimulation group

	Sham group (n=69)			taVNS group (n=73)				
	Baseline	Week 12	Change	Baseline	Week 12	Change	Absolute between-group difference in change (95% CI)	p value
Primary endpoint in the intention-to-treat population								
VAS hand pain score, mm	58·6 (18·9)	50·0 (24·9)	–8·6 (28·3)	60·6 (18·0)	46·2 (22·2)	–14·4 (28·2)	–5·8 (–15·2 to 3·6)	..
VAS hand pain score, mm	60·0 (49·0 to 72·0)	53·0 (26·0 to 66·0)	–6·0 (–27·0 to 7·0)	63·0 (51·0 to 73·0)	52·0 (31·0 to 60·6)	–16·0 (–32·0 to 5·0)	–10·0 (–23·0 to 2·0)	0·22*
Secondary endpoints in complete case population								
AUSCAN pain score, 0–100†	62·9 (16·1)	51·7 (21·8)	–11·0 (17·9)	62·1 (14·3)	50·5 (17·7)	–12·0 (17·7)	–1·0 (–7·2 to 5·3)	0·76‡
AUSCAN stiffness score, 0–100†	60·1 (26·2)	54·7 (28·1)	–6·3 (30·2)	61·0 (22·4)	52·4 (26·1)	–8·7 (24·2)	–2·5 (–12·1 to 7·1)	0·61‡
AUSCAN function score, 0–100†	66·9 (19·1)	59·1 (24·6)	–8·2 (19·3)	64·2 (17·5)	53·8 (20·0)	–10·5 (17·2)	–2·4 (–8·8 to 4·0)	0·47‡
FIHOA score, 0–100†	45·0 (21·5)	46·6 (23·0)	2·4 (16·9)	45·2 (19·4)	40·2 (18·7)	–4·9 (15·6)	–7·3 (–13·0 to –1·6)	0·013‡
Cochin hand score, 0–90§	25·9 (17·7)	26·5 (18·8)	0·4 (14·1)	23·4 (15·4)	20·3 (16·1)	–2·4 (12·4)	–2·8 (–7·5 to 1·9)	0·24‡
DN4 score¶	3·4 (1·9)	2·5 (1·7)	–1·0 (2·2)	3·4 (2·0)	2·7 (2·1)	–0·9 (1·9)	0·1 (–0·6 to 0·9)	0·73‡
HAD score, 0–21¶	9·1 (3·8)	8·0 (4·1)	–0·9 (2·9)	9·1 (3·9)	8·3 (4·4)	–0·5 (2·7)	0·5 (–0·5 to 1·5)	0·34‡
EQ-D5-3L score¶	0·59 (0·25)	0·63 (0·26)	0·06 (0·20)	0·58 (0·27)	0·66 (0·24)	0·07 (0·22)	0·02 (–0·06 to 0·09)	0·64‡
Patient global assessment score, 0–100†‖	63·7 (21·0)	61·2 (23·8)	–3·8 (20·0)	59·2 (22·9)	66·3 (19·1)	6·9 (25·9)	10·7 (2·6 to 18·9)	0·010‡
VAS fatigue score, 0–100†	44·1 (26·6)	40·1 (28·6)	–3·7 (30·8)	45·6 (28·1)	44·3 (27·4)	–2·9 (34·0)	0·8 (–10·6 to 12·2)	0·89‡
Number of painful joints, 0–30¶	9·3 (5·8)	7·1 (5·0)	–2·4 (4·4)	8·2 (4·3)	6·8 (4·6)	–1·7 (4·4)	0·7 (–0·8 to 2·3)	0·36‡
Number of swollen joints, 0–30¶	3·8 (2·4)	3·9 (3·4)	0·1 (3·1)	4·4 (3·0)	4·2 (3·7)	–0·4 (3·9)	–0·5 (–1·7 to 0·8)	0·47‡
Patient acceptable symptom state¶	..	22/64 (34%)	..	..	31/63 (49%)	..	15 (–3 to 32)	0·13**
OARSI–OMERACT responders†	..	18/64 (28%)	..	..	22/63 (35%)	..	7 (–10 to 23)	0·53**
Patient global impression of change¶	..	15/63 (24%)	..	..	21/63 (33%)	..	10 (–7 to 26)	0·32**
Paracetamol consumption, g/day††	..	0·07 (0·01 to 0·23)	..	..	0·10 (0·02 to 0·36)	..	0·03 (–0·04 to 0·12)	0·28*

Data are n/N (%), mean (SD), or median (IQR), unless otherwise specified. AUSCAN=Australian–Canadian Osteoarthritis. DN4=neuropathic pain score. FIHOA=Functional Index of Hand Osteoarthritis. HAD=hospital anxiety and depression score. OARSI=Osteoarthritis Research Society International. OMERACT=Outcome Measures in Rheumatology. taVNS=transcutaneous auricular vagus nerve stimulation. VAS=visual analogue scale. *Wilcoxon rank-sum test. †Five missing values in the sham group and ten missing in the taVNS group. ‡Student *t* test. §Seven missing values in the sham group and ten missing in the taVNS group. ¶Six missing values in the sham group and ten missing in the taVNS group. ‖Higher scores indicate better health. **χ^2 test with Yates' continuity correction. ††Eight missing values in the sham group and ten missing in the taVNS group.

***Table 2*: Primary and secondary clinical outcomes at baseline, week 12, and change from baseline to week 12**

completed the 12-week study and were included in the intention-to-treat analysis with available data. Three (4%) of 69 patients in the sham group and seven (10%) of 73 in the taVNS group discontinued the study because of tolerance issues (appendix p 4). After excluding 37 patients (18 [26%] of 69 in the sham group and 19 [26%] of 73 in the taVNS group) because of major deviations from the protocol (appendix p 5), the per protocol population included 105 patients (51 [74%] of 69 in the sham group and 54 [74%] of 73 in the taVNS group).

Overall, the mean age was 66·5 years (SD 8.4), 125 (88%) of 142 participants were female, and 17 (12%) were male. The mean BMI was 24·9 kg/m² (SD 4·9). Baseline characteristics were well balanced between the groups (table 1) and did not differ substantially for participants who stopped the treatment before the end of the study (at 12 weeks; appendix p 6).

At week 12, taVNS resulted in a reduction in median VAS hand pain score of –16·0 (IQR –32·0 to 5·0) compared with –6·0 (–27·0 to 7·0) in the sham group, with a between-group difference of –10·0 (95% CI –23·0 to 2·0; p=0·22; table 2) but this difference was not significant (figure 2A). In sensitivity analyses, similar results were obtained in the intention-to-treat population with available data (–22 [–36·0 to 0·0]; n=63 *vs* –6 [–29·0 to 8·0]; n=64; difference –16·0 [–27·0 to –6·0; p=0·072) and in the per protocol population (–20·5 [–34·0 to –1·0]; n=54 *vs* –7·0 [–32·0 to 5·0]; n=51; difference –13·5 (–26·5 to 1·5; p=0·19; appendix p 7). Similarly, the results of the linear mixed model taking into account centre and baseline VAS value were consistent, showing no effect of treatment on VAS pain score at week 12.

At week 12, we found a decrease in mean FIHOA score of –4·9 (SD 15·6) in the taVNS group compared with an increase of 2·4 (16·9) in the sham group, with a significant between-group difference of –7·3 (95% CI –13·0 to –1·6; p=0·013; table 2; figure 2B). Patients in the taVNS group had an improvement in mean patient global assessment score of 6·9 (25·9) compared with a decrease of –3·8 (20·0) in the sham group, with a significant difference of 10·7 (2·6 to 18·9; p=0·010). We found no between-group differences in the mean AUSCAN pain, stiffness, or function sub-scores; Cochin hand score; EQ-D5 score; HAD score; VAS fatigue score;

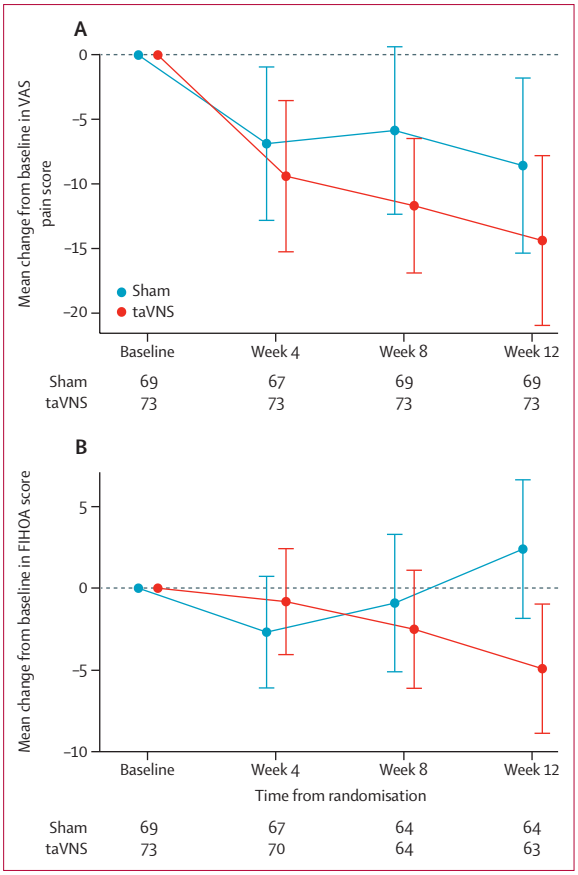

Figure 2: **VAS pain score and FIHOA score over 12 weeks in the intention-to-treat population**
(A) VAS pain score. (B) FIHOA score. Dots represent the mean change at each timepoint relative to randomisation. Error bars represent 95% CIs. taVNS=transcutaneous vagus nerve stimulation. VAS=visual analogue scale. FIHOA=Functional Index of Hand Osteoarthritis.

number of painful and swollen joints; and DN4 score (table 2). We found no significant between-group difference in the proportions of patients who met the OARSI OMERACT response criteria and patient global impression of change score. A numerically higher proportion in the taVNS group reached a patient acceptable symptom state (31 [49%] of 63) than in the sham group (22 [34%] of 64) but this difference was also non-significant (p=0·13). Baseline consumption of paracetamol was low (59 [42%] of 142 patients; median 2 g/week [IQR 1·0 to 4·0] in consumers) and did not differ between groups at week 12 (table 2).

The median concentration of coll2-1 NO_2 decreased in the taVNS group by –8·7% (IQR –18·3 to 9·1), whereas the value increased by 0·2% (–11·3 to 17·4) in the sham group, with a non-significant difference of –8·9% (–17·3 to 0·4). We found no difference for inflammatory biomarkers (hs-CRP, IL-6, IL-8, and TNF concentrations) and coll2-1 (appendix p 8). 13 (9%) of 142 patients at baseline and eight (6%) patients at week 12 had a hand MRI. Synovitis decreased in one (25%) of four patients in the taVNS group

	Sham group (n=69)	taVNS group (n=73)	Absolute between-group difference (95% CI)
At least one non-serious adverse event	16 (23%)	22 (30%)	7% (–8 to 22)
At least one local dermatological irritation event	3 (4%)	3 (4%)	..
At least one local mild pain event	4 (6%)	8 (11%)	..
At least one tingling of the ear event	1 (1%)	11 (15%)	..
At least one other adverse event	12 (17%)	9 (12%)	..

Data are n (%), unless otherwise specified. taVNS=transcutaneous auricular vagus nerve stimulation.

Table 3: **Adverse events**

over 12 weeks and three (75%) of four patients in the sham group. Bone marrow lesions decreased in one (25%) of four patients in the taVNS group and in two (50%) of four patients in the sham group (appendix p 9). Adherence to the treatment regimen was good, with a mean daily use duration of 20·1 min (SD 0·5) in the taVNS group and 19·6 min (2·0) in the sham group over the 12-week period. The mean intensity used over the 12 weeks was 7·3 mA (1·2) in the taVNS group and 7·9 mA (2·3) in the sham group.

No serious adverse events were observed. Overall, 38 (27%) of 142 patients had at least one non-serious adverse event between day 0 and week 12 (16 [23%] of 69 participants in the sham group and 22 [30%] of 73 in the taVNS group; difference 7% [95% CI –8 to 22]; table 3). The main adverse effects reported included mild local pain, dermatological irritation, and uncomfortable tingling sensations at the earpiece.

In exploratory analyses, taVNS showed no effect on WOMAC hip or knee pain scores compared with sham stimulation in patients who declared having knee or hip osteoarthritis (appendix p 10). A high proportion of participants in the taVNS group (54 [86%] of 63) and sham group (57 [89%] of 64) found the device easy or very easy to use. More patients in the taVNS group (51 [81%]) reported greater satisfaction with the treatment compared with the sham group (35 [55%]). 39 (63%) of 62 patients in the taVNS group believed they received active vagus nerve stimulation compared with 23 (38%) of 61 in the sham group (appendix p 11).

Exploratory subgroup efficacy analyses revealed that in patients with at least two joints with ultrasound synovitis, taVNS (58 [79%] of 73 participants) reduced the median VAS pain score by –22·5 mm (IQR –35·0 to –0·5) compared with –6·5 (–31·0 to 7·0) in those receiving sham stimulation (56 [81%] of 69) with a median difference of –16·0 (95% CI –27·0 to –2·5; appendix pp 12–13). Additionally, in patients with at least five joints with ultrasound synovitis (median), taVNS (35 [48%] of 73 participants) reduced the median VAS pain score by –28·0 (–41·5 to –2·5) compared with –9·0 (–36·0 to 3·0) in those receiving sham stimulation (36 [52%] of 69 participants), with a median difference of –19·0 (95% CI –30·5 to –1·0; appendix pp 12–13). Similar results were observed in patients with at least four joints

with clinical synovitis and those in the middle or highest FIHOA score tertile (appendix 13). Other subgroup analyses revealed numerically greater improvement in VAS hand pain scores with taVNS compared with sham stimulation in certain prespecified groups (eg, patients with a DN4 score ≥3 or ≥2 joints with clinical synovitis), with moderate effect sizes but wide CIs crossing the null (appendix p 13). By contrast, some subgroups showed minimal or no apparent differences between treatment groups for hand VAS pain score and OMERACT-OARSI response (appendix pp 13–14). Lastly, no correlation was found between baseline biomarker levels and the change in VAS pain score within the active taVNS group (appendix 15).

Discussion

In this randomised, sham-controlled, multicentre, double-blind study, taVNS did not significantly decrease pain in participants with erosive and inflammatory hand osteoarthritis over 12 weeks compared with sham stimulation in the intention-to-treat population. However, taVNS was associated with improved function and patient global assessment score. Furthermore, exploratory analysis highlighted a more pronounced pain reduction in patients with greater joint inflammation. Tolerance was similar between groups, with no serious adverse events reported.

This study is a proof-of-concept study as it is the first randomised controlled trial of vagus nerve stimulation in patients with hand osteoarthritis. Studies suggest vagal dysfunction in patients with osteoarthritis, with reduced high-frequency heart rate variability indicating a loss of vagal tone.[21] Also, greater hand and knee osteoarthritis severity is associated with higher heart rates independent of age, sex, physical activity, and comorbidities.[22] Although vagus nerve stimulation has not been studied in preclinical osteoarthritis models, the absence of α7nAchR exacerbates disease severity, whereas systemic nicotine—an α7nAchR agonist—attenuates pain and structural damage.[23] In clinical settings, an open-label pilot study[24] in 30 patients with knee osteoarthritis showed short-term pain reduction with taVNS. Similarly, a previous open-labelled study[14] in 18 patients with inflammatory erosive hand osteoarthritis reported pain and functional improvements after 4 weeks of taVNS, without safety concerns. Altogether, these findings provided the rationale for the ESTIVAL trial.

In this study, 12 weeks of taVNS did not significantly decrease erosive hand osteoarthritis pain compared with sham stimulation in the overall population. One possible explanation might be a lack of effect on the vagus nerve. Stimulation targeted the cymba conchae, innervated by the auricular branch of the vagus nerve, which showed brainstem activation in functional MRI studies.[11] We used a 25 Hz frequency, as in the study by Yakunina and colleagues,[11] which showed activation of the nucleus tractus solitarius, a key structure in the vagal pathway, by cymba concha stimulation. This frequency has also been used in other studies involving patients with rheumatic diseases. However, the pulse width of the device (100 μs) was lower than in other studies (300–500 μs), possibly limiting stimulation intensity.[25] This setting was selected in consultation with the manufacturer to balance efficacy and tolerability and to maintain masking. However, doing so modulates the maximum intensity used and could affect the overall intensity of stimulation. Stimulation parameters of taVNS remain heterogeneous across studies, including frequency, intensity, and pulse width.[12,25] Additionally, we chose a 20-min daily duration for feasibility, on the basis of previous studies, although durations vary widely across trials—from seconds to several hours—and no optimal protocol has been established.[14]

Despite the non-significant effect on pain, taVNS improved function (with a significant reduction in FIHOA score) and patient global assessment score over sham stimulation, both key outcomes in erosive hand osteoarthritis. taVNS has shown benefits on patient-reported outcomes in other rheumatic diseases, including improvements in pain and fatigue in small trials in systemic lupus erythematosus, systemic sclerosis, and Sjögren's disease.[25] However, a large randomised controlled trial in rheumatoid arthritis indicated that taVNS did not show significant clinical improvement.[25] This finding might also be explained by differences in settings since a very high frequency of 20 kHz was used. Ongoing trials will help clarify the role of vagus nerve stimulation in rheumatology and guide optimisation of stimulation parameters.

Another explanation for the lack of pain reduction might be suboptimal patient selection. Although all participants had at least one inflamed joint, sensitivity analyses suggested greater analgesic effects of taVNS over sham stimulation in those with two or more joints with ultrasound-detected synovitis, with a dose effect since effect increased in patients with five or more joints with ultrasound-detected synovitis. As vagus nerve stimulation modulates inflammation via acetylcholine release and α7nAchR signalling, particularly in splenic macrophages, patients with greater joint inflammation might be more responsive.[26] Future randomised controlled trials on taVNS should specifically target patients with higher inflammatory activity.

In the intention-to-treat population, taVNS did not affect clinical (swollen joints) or systemic inflammatory markers (cytokines). Although implantable and taVNS reduces cytokine (mostly TNF and IL-6) production in lipopolysaccharide stimulated blood from healthy individuals and patients with rheumatic diseases, such effects might not be detectable in populations with low baseline cytokine concentrations or in the absence of an ex vivo inflammatory trigger.[12,27] This discrepancy is possibly due to the low concentration of circulating pro-inflammatory cytokines in this population. However,

changes in cytokine concentrations are not correlated with clinical efficacy since taVNS might improve symptoms such as fatigue or pain without inducing biological effects—eg, in systemic lupus erythemtosous.[28]

Finally, we confirmed the good safety profile of taVNS, with no serious adverse events. Non-serious adverse events occurred in 38 (27%) of 142 patients, mostly local ear reactions, with no difference between the two groups. No bradycardia was observed, consistent with left-sided stimulation, which avoids cardiac innervation. These findings align with previous taVNS studies in rheumatic diseases and support the intervention's safety in comorbid osteoarthritis populations.

This study has limitations. We chose a sham group without stimulation, whereas others used low-frequency stimulation (1 Hz) or stimulation at other sites (eg, the earlobe). We chose this modality because even low stimulation can stimulate the vagus nerve, as shown in previous studies.[11] Stimulation at another site carries an increased risk of unmasking investigators and patients. The main masking bias here could be the appearance of symptoms such as tingling or local electrical discharges between the two groups. To minimise this risk, we provided identical instructions to ensure identical device explanations between groups. We also analysed clinical efficacy before safety. 23 (36%) of the 61 participants in the sham group thought they were in the active group, most likely due to non-specific sensations caused by the application of the device and conductive gel, which can mimic active stimulation. This perception bias has been frequently reported in neuromodulation trials, including those using transcutaneous electrical nerve stimulation or taVNS.[29,30] Second, dropout rates were slightly higher in the taVNS group than in the sham group (ten [13%] of 73 patients in the taVNS group *vs* five [7%] of 69 patients in the sham group), but were overall similar to those of other randomised controlled trials in hand osteoarthritis.[6,7] Also, we might have underestimated the SD in our sample size calculation as the analgesic response varied more than expected. However, we used data from our pilot study to calculate the SD used to calculate the sample size.[14] This potential underestimation could have reduced our capacity to detect a difference between the groups with 142 patients. Furthermore, the MRI sample size is too small to draw any conclusions regarding the effect of taVNS on joint inflammation, regardless of the direction of change. Additionally, although we integrated patient perspectives from the ADEPT pilot study to inform the trial design[14] and collaborated with the French patient association AFLAR for study dissemination, no individuals with lived experience were directly involved in reviewing study materials, contributing to the research process, or in the dissemination of findings. Finally, the study did not collect data on participants' ethnicity and did not perform sex-disaggregated analyses, which might limit the generalisability of the findings to more diverse populations.

This study also has several notable strengths. It was a robustly designed, randomised, controlled, multicentre, double-blind trial. We included many patients compared with other randomised controlled trials on taVNS. We selected a homogeneous and well-characterised population with inflammatory erosive hand osteoarthritis coming from active hospital files, private practice rheumatology clinics, as well as from the general public. We confirmed inflammation using baseline ultrasound. Thanks to the device-use tracker, we ensured that patients had good adherence to taVNS without any difference between the groups. Finally, we enrolled all patients in 11 months instead of 24 months, showing the huge demand of patients and the unmet need of effective treatment in erosive hand osteoarthritis.

In conclusion, the ESTIVAL trial did not show a significant analgesic effect of taVNS in patients with erosive and inflammatory hand osteoarthritis over 12 weeks. However, the findings provide a rationale for further studies of taVNS in patients with more inflammatory forms of erosive hand osteoarthritis—eg, those with at least two joints with synovitis. Further research is also warranted to better optimise the stimulation settings and understand the underlying mechanisms of action.

Contributors

AC, ST, AT, AR, TS, FB, and JS conceptualized and designed the study. AC, ST, CN, AT, AR, TS, FB, and JS drafted the original protocol. JS obtained the funding. JS coordinated the study. AC, ST, GC, CH R, PO, Y-MP, J-EG, EL, RC, DA, FR, DW, FE, SM, PR, AS, HM, NP, A-CR, J-PB, SF, YH, LM, CD, CN, AT, AR, TS, EM FB, JS acquired the data. AC, JS, ST, and AR designed the statistical analysis plan. AC, ST, AR, and JS verified the data. ST and AR accessed the raw data and directly accessed and verified the underlying data reported in the manuscript. EM performed radiographs readings and LM the MRI scorings. AC, JS, ST, and AR analysed and interpreted the data. AC drafted the original manuscript. AC, ST, GC, CH R, PO, Y-MP, J-EG, EL, RC, DA, FR, DW, FE, SM, PR, AS, HM, NP, A-CR, J-PB, SF, YH, LM, CD, CN, AT, AR, TS, EM FB, JS reviewed and provided comments on the manuscript. All authors approved the final version and had final responsibility for the decision to submit for publication. All authors had full access to all the data in the study and take responsibility for the integrity of the work as a whole, from inception to finished Article.

Declaration of interests

AC reports consulting fees from Janssen, AbbVie, and UCB; honoraria from AbbVie, Pfizer, and Lilly; and travel support from Pfizer, Roche, AbbVie, UCB, Bristol Myers Squibb (BMS), Novartis, Janssen, IBSA Pharma, and Biogen. FE reports grants or contracts from REGENLAB; consulting fees from NORDIC Pharma; honoraria from Novartis, Expanscience, Alfasigma, Galapagos, MSD, BMS, IBSA, and Pfizer; travel support from UCB, Novartis, NORDIC Pharma, and FIDIA; and participation on an advisory board for LABRHA. EM reports consulting fees from Carilène, TRB Chemedica, and Expanscience; honoraria from FIDIA, IBSA Pharma, Pierre Fabre, and Sublimed; travel support from TRB Chemedica and IBSA Pharma; and advisory board participation for Sublimed. HM reports consulting fees and honoraria from AbbVie, Biogen, BMS, Celltrion, Fresenius Kabi, Galapagos, Janssen, Lilly, Medac, NORDIC Pharma, Novartis, Pfizer, and UCB. SM reports honoraria from Tilman, and travel support from Biogen, Lilly, Amgen, and MSD. JS reports institutional support from the French Ministry of Health (Direction Générale de l'Offre de Soins), via the national Programme Hospitalier de Recherche Clinique, for conducting the ESTIVAL study, reports research grant from Pfizer and honoraria from AbbVie, AlfaSigma, Axomove, Fresenius Kabi, Grünenthal, Guerbet,

IBSA Pharma, Janssen, Lilly, Nordic Pharma, Novartis and UCB. YH reports serving as Chair of the Scientific Board of Artialis, provider of the coll2-1 and coll2-1NO2 biomarkers used in the study. FB reports consulting fees from Grünenthal, GSK, Eli Lilly, Novartis, Pfizer, Servier, and 4P Pharma; honoraria from Viatris, Pfizer, and Zoetis; travel support from Nordic Pharma; advisory board participation for AstraZeneca, Sun Pharma, and Nordic Bioscience; and stock ownership in 4P Pharma and 4Moving Biotech. All other authors declare no competing interests.

Data sharing

Due to privacy and consent restrictions, the data generated from this study will not be uploaded to a public repository. De-identified data will be made available from the corresponding author to researchers on reasonable request, subject to a data sharing agreement.

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