


# BMJ Open Transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: protocol for the randomised, double-blind, sham-controlled ESTIVAL trial

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## ABSTRACT

**Introduction** Patients with erosive hand osteoarthritis (EHOA) experience pain and inflammation, two features that can be targeted by vagus nerve stimulation using electrical auricular transcutaneous vagus nerve stimulation (tVNS). A pilot study demonstrated the feasibility of the procedure, so we designed a randomised sham-controlled trial to determine the safety and efficacy of tVNS in EHOA.

**Methods and analysis** ESTIVAL Study (Essai randomisé comparant la Stimulation auriculaire transcutanée du nerf Vague versus sham stimulation dans l'Arthrose Digitale Érosive symptomatique et inflammatoire) is a superiority, randomised, double-blind sham-controlled trial comparing two parallel arms: active and sham tVNSs in a 1:1 ratio. Patients with symptomatic EHOA (score  $\geq 40/100$  mm on a visual analogue scale (VAS) for pain of 0–100 mm) and inflammatory EHOA ( $\geq 1$  clinical and ultrasonography-determined interphalangeal synovitis) are included in 18 hospital centres (17 rheumatology and 1 rehabilitation departments) in France. Active and sham tVNSs use an auricular electrode connected to the Vagustim device, with no electric current delivered in the sham group. Patients undergo stimulation for 20 min/day for 12 weeks. The follow-up visits take place at weeks 4, 8 and 12. The enrolment duration is 2 years and started in April 2021; 156 patients are scheduled to be included. The primary outcome is the difference in self-reported hand pain in the previous 48 hours measured on a VAS of 0–100 mm between baseline and week 12. Secondary outcomes include other pain outcomes, function, quality of life, serum biomarker levels, compliance and tolerance. For a subset of patients, MRI of the hand is performed at baseline and week 12 to compare the change in Outcome Measures in Rheumatology/Hand Osteoarthritis MRI Scoring System subscores. The primary analysis will be performed at the end of the study according to the intent-to-treat principle.

**Ethics and dissemination** Ethics approval was obtained from the institutional review board (Comité de Protection des Personnes, 2020-A02213-36). All participants will be required to provide written informed consent. The findings will be published in peer-reviewed journals.

**Trial registration number** NCT04520516; Pre-results.

**Protocol version and number** V.2 of 11 March 2021.

## Strengths and limitations of this study

- The ESTIVAL study (Essai randomisé comparant Stimulation auriculaire transcutanée du nerf Vague versus sham stimulation dans l'Arthrose digitale érosive symptomatique et inflammatoire) is a large, multicentre, randomised controlled study that will provide data on an innovative treatment for erosive hand osteoarthritis (EHOA).
- A clinical, biological and imaging evaluation is planned to evaluate the efficacy of active auricular transcutaneous vagus nerve stimulation (tVNS) as compared with sham tVNS in symptomatic and inflammatory EHOA.
- Limitations can be due to blinding quality because some dysesthesia can be reported with tVNS, but several procedures will mitigate this issue as much as possible.

## INTRODUCTION

Among all locations of osteoarthritis (OA), symptomatic hand osteoarthritis (HOA) is frequent, affecting 8.2% of men and 16% of women in the general population older than 50 years.<sup>1</sup> Erosive hand osteoarthritis (EHOA) is a severe HOA subset, defined by the presence of central erosions and collapse of the subchondral bone plate on X-rays.<sup>2</sup> EHOA frequency varies, depending on the population studied: 2.8% in the general population over age 55 years and 3.6%–10.2% in HOA populations but could reach 25%–50% of symptomatic patients with HOA in secondary care centres.<sup>1,3–6</sup>

The main characteristics of EHOA are the higher level of pain and more inflammatory features than non-erosive HOA.<sup>3,4,7</sup> Patients with EHOA could even experience more articular symptoms than those with inflammatory arthritis.<sup>8</sup> Inflammation characterised



by joint clinical soft swelling or erythema (ie, synovitis) occurs more frequently in EHOA than in non-erosive HOA according to clinical assessment, ultrasonography (US) or MRI.<sup>9–11</sup> As well, ultra sensitive C reactive protein (usCRP) level is higher in EHOA than non-erosive HOA and is correlated with the number of painful or tender joints.<sup>12</sup>

Despite its burden and frequency, EHOA lacks effective treatments. Recent trials investigating hydroxychloroquine, colchicine and synthetic or biological disease-modifying antirheumatic drugs (DMARDs) give disappointing results.<sup>13–17</sup> A recent study showed that 6 weeks of 10mg prednisolone per day was superior to placebo for HOA symptoms with inflammatory features, but this finding raises safety issues.<sup>18</sup> Hence, innovative therapies are expected.

Vagus nerve stimulation (VNS) could be a novel therapy because it may decrease the inflammation and pain. The binding of acetylcholine, the main mediator of the vagus nerve (VN), to one of its receptors, nicotinic acetylcholine alpha-7 receptor, decreases systemic tumour necrosis factor (TNF) production.<sup>19–20</sup> As well, afferent VNS signalling towards central nervous system (CNS) centres could limit pain signals and regulate the hypothalamic–pituitary–adrenal axis.<sup>21</sup>

Invasive VNS has shown promising results, with an anti-inflammatory effect in rheumatoid arthritis or inflammatory bowel disease.<sup>22–25</sup> More recently, non-invasive VNS has included auricular transcutaneous vagus nerve stimulation (tVNS), which stimulates a sensitive afferent branch of the VN located in the ear (the *cymba concha*).<sup>26</sup> tVNS is being evaluated in several chronic painful and inflammatory diseases.<sup>27</sup>

In an open-label pilot study, we showed that 1-hour auricular tVNS per day significantly decreased pain and the number of tender and swollen joints and improved function in 18 patients with EHOA, but more importantly was well tolerated.<sup>28</sup> However, the low number of patients and no control group could not allow us to rule out a placebo effect for effectiveness.

Therefore, in this superiority study, we aimed to assess the efficacy and safety of tVNS for EHOA symptoms versus sham tVNS in a multicentre randomised trial. We hypothesise that as compared with sham stimulation, tVNS will decrease hand pain and improve hand function in patients with EHOA.

## METHODS AND ANALYSIS

### Study design

ESTIVAL (Essai randomisé comparant STimulation auriculaire transcutanée du nerf Vague versus sham stimulation dans l'Arthrose digitale érosive symptomatique et inflammatoire) is a superiority double-blinded multicentre and sham-controlled randomised trial comparing two parallel arms. A total of 18 centres, all involved in caring for patients with EHOA, are participating in this trial. The sponsor is the Assistance Publique–Hôpitaux

de Paris (Délégation à la Recherche Clinique et à l'Innovation). The trial is funded by a grant from Programme Hospitalier de Recherche Clinique 2019 (French Ministry of Health). The study is conducted in accordance with the Declaration of Helsinki and has been approved by an ethics committee (Ile de France, number 2020-A02213\_36). The protocol follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.<sup>29–30</sup> ESTIVAL is registered at ClinicalTrials.gov.

All patients included undergo the auricular tVNS with the Vagustim or sham treatment with the same device, which has the same appearance but does not deliver any electric current. Patients are randomised to receive the active or sham tVNS for 12 weeks with no crossover design. Each patient is scheduled for a visit at baseline and at 4, 8 and 12 weeks (figure 1). At each visit, patients complete questionnaires and undergo a clinical examination for efficacy and safety assessments (table 1). An 8.5mL blood sample is collected at baseline and at the 12-week visit. Patients followed up in Saint-Antoine Hospital Center undergo non-contrast MRI of the most symptomatic hand at the baseline visit and week 12.

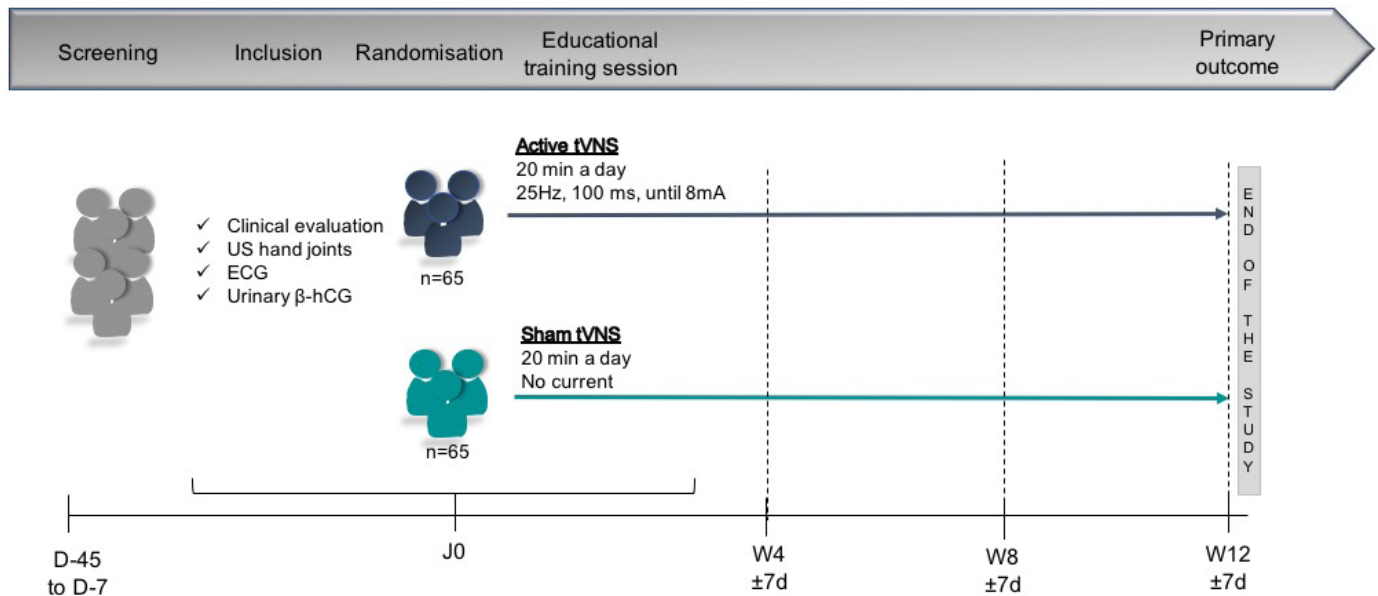
### Study participants

Patients are recruited during outpatient visits in each centre. During a screening visit, patients who fulfil inclusion criteria are informed about the trial and the protocol. They are informed about the two arms of the protocol and that they might be in the sham group. The investigator confirms the selection criteria (radiographic EHOA and presence of at least one joint with soft swelling or erythema, ie, synovitis) and then proposes the trial to the patient. If the patient agrees to participate, an inclusion visit is planned, and the patient is told to stop taking non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen 48 hours before the inclusion visit.

The inclusion visit is conducted by a medical doctor and includes checking inclusion and non-inclusion criteria, the patient giving informed written consent, a physical examination, completing questionnaires, hand US (to look for interphalangeal (IP) synovitis), electrocardiography, an urinary beta-human chorionic gonadotropin test for women of childbearing age, an 8.5mL blood sample taken and bilateral anteroposterior hand radiography (table 2). A subset of patients, all included in Saint-Antoine Hospital Center, undergo MRI of the most symptomatic hand at IP joints.

### Inclusion, exclusion and randomisation criteria

The study includes patients aged  $\geq 18$  years with symptomatic HOA according to the American College of Rheumatology criteria and EHOA (defined by  $\geq 1$  erosive digital joint based on Verbruggen-Veys hand radiographic scoring).<sup>2–31–32</sup> Patients must have pain intensity of the hand of  $\geq 40/100$ mm on a visual analogue scale (VAS) at inclusion at least half of the last 30 days, at least  $\geq 1$  symptomatic proximal or distal IP (proximal or distal IP) joint with clinical soft swelling or erythema at inclusion,



**Figure 1** Schematic flow of the design of the randomised study comparing symptomatic effects of auricular tVNS versus sham tVNS in patients with symptomatic and inflammatory EHOA. Patients with symptomatic EHOA and inflammatory clinical and ultrasonography-evidenced synovitis are randomised (1:1) to active tVNS (n=65) or sham tVNS (n=65) for 20 min each day for 12 weeks. The two treatment arms are assessed at 4, 8 and 12 weeks. The primary outcome is assessed at 12 weeks. β-hCG, β-human Chorionic Gonadotropin; EHOA, erosive hand osteoarthritis; tVNS, transcutaneous vagus nerve stimulation.

and reported adverse effects with or inadequate response or contraindication to existing medication (including acetaminophen, topical and oral NSAIDs). Additionally, patients must give informed written consent (online supplemental file 1) and must be affiliated with a social security scheme. Exclusion criteria are in [table 1](#).

To be randomised, included patients must also have the following:

- ▶ At least  $\geq 1$  proximal or distal IP joint with presence of moderate or major grey scale synovitis (score 2 or 3) and/or power Doppler signal (score  $\geq 1$ ) on hand joint US.
- ▶ No contraindication to tVNS use, diagnosed on electrocardiography at inclusion (cardiac rhythm disturbances, atrioventricular block of >first degree or total bundle branch block >120 ms).
- ▶ Negative urine pregnancy test at inclusion, if appropriate.

### Interventions

The trial intervention is auricular active or sham tVNS for 20 min/day, every day for 12 weeks. Staff at each centre receive a training session by the main investigator or the clinical researcher associate (CRA) about the device and settings, how to use the device and how to explain its use to the patient to maintain blinding.

The tVNS device pack was graciously provided by Schwa-Medico (Rouffach, France) and contains the following ([figure 2](#)):

- ▶ The Vagustim device (EC certificate, registration number DD 60136841 0001; report number 28417062 004 dated 4 March 2019, CE0197-2020/04/28), which is a transcutaneous electrical nerve stimulation

(TENS) device from Schwa-Medico especially designed to connect to an ear electrode. The waveform is biphasic, asymmetrically balanced, with amplitude from 0 to 99 mA. Frequency preset modes are at 25, 10 and 1 Hz and will be set at 25 Hz, 100  $\mu$ s.

- ▶ One auricular electrode (Monath Electronic).
- ▶ Conductive gel medical device (C+V Pharma Depot GmbH, Versmold, Germany).

To properly stimulate the VN, a conductive gel is applied on the auricular electrode to ameliorate electrical transmission. The electrode is then applied on the left cymba concha for each daily use. The tVNS is performed on the left ear because efferent fibres to the heart that innervate the sinoatrial node are located on the right side and so could be connected to the VN afferent fibres of the right ear.<sup>23</sup> The participants randomised in the sham group receive the same device pack with a Vagustim device that looks exactly the same. The active and sham devices look exactly the same. All the procedures and daily settings are exactly the same for both devices; all patients will wear the auricular electrode with conductive gel, turn on the device, will see the same screen and will set the intensity to a maximum of 8 mA or less if they feel discomfort. For the sham device, the intensity will appear as a real intensity, but no current will be delivered.

After randomisation, the patients are thoroughly instructed in how to use the device, and the first active session is performed at the hospital. This training session is performed by a nurse, another medical doctor or the clinical research technician at the baseline visit and, if necessary, at visits on weeks 4 and 8. Furthermore, the person who performs the training calls the patient to

**Table 1** Exclusion criteria of ESTIVAL study (Essai Randomisé Comparant Stimulation Auriculaire Transcutanée du nerf Vague versus Sham Stimulation dans l'Arthrose Digitale Érosive Symptomatique et Inflammatoire)

Exclusion criteria	<ul style="list-style-type: none"> <li>▶ Isolated or a predominant pain thumb-base OA.</li> <li>▶ Other inflammatory joint disease (eg, gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis and Lyme disease), psoriasis, current skin disease of the left ear (eg, eczema, urticarial lesion, skin infection and external otitis).</li> <li>▶ Ear canal not adapted to apply the auricular electrode.</li> <li>▶ Known history of cardiac rhythm disturbances, atrioventricular block &gt;first degree or total bundle branch block.</li> <li>▶ Symptomatic orthostatic hypotension or repeated vasovagal syncope history and history of vagotomy.</li> <li>▶ Severe asthma and treated sleep apnoea.</li> <li>▶ Evidence of serious uncontrolled concomitant medical condition (including cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, gastrointestinal disease or epilepsy), which in the opinion of the investigator makes them unsuitable for the study.</li> <li>▶ Pregnant or breast feeding.</li> <li>▶ Existence of a pain syndrome of the upper limbs that would interfere with the monitoring of pain or fibromyalgia.</li> <li>▶ Use of other electrically active medical devices (eg, pacemaker or transcutaneous electrical nerve stimulation for chronic pain).</li> <li>▶ Use of oral/intramuscular or intra-articular or intravenous corticosteroids, disease-modifying antirheumatic drugs (eg, slow-acting antirheumatic drugs such as methotrexate and sulfasalazine) or intra-articular hyaluronic acid to the hand joints within the last 3 months.</li> <li>▶ Any new hand OA treatment in the previous 2 months (including physiotherapy or orthosis), planned hand surgery in the next 3 months or use of any investigational (unlicensed) drug within 3 months before screening.</li> <li>▶ Patients under legal protection measure (tutorship or curatorship) and patients deprived of freedom.</li> <li>▶ Use of vagus nerve stimulation before the study.</li> <li>▶ Use of non-steroidal anti-inflammatory drugs or acetaminophen less than 48 hours before the inclusion visit.</li> </ul>
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OA, osteoarthritis.

check on the proper use of the device at  $10 \pm 7$  days after the baseline visit.

Three parameters are set:

- ▶ Frequency at 25 Hz.
- ▶ 100  $\mu$ s.
- ▶ Intensity is progressively increased from 0 to 8 mA during the daily setting. If the patient starts to feel discomfort, the intensity level below this uncomfortable intensity is selected to obtain a non-painful and non-unpleasant intensity.

Then patients self-administer their treatment using the device for 20 min/day for 12 weeks. The following pain

treatments are allowed: acetaminophen (except during the 48 hours before each visit), hand orthosis if used for more than 2 months before inclusion, and physiotherapy or occupational therapy if prescribed at least 2 months before inclusion and stable during the trial. Topical or oral NSAIDs, opioids, hand surgery and hand joint infiltration (corticosteroids and hyaluronic acid) are prohibited.

Patients come for a medical visit every 4 weeks for 12 weeks (weeks 4, 8 and 12). At each visit, participants undergo hand and general clinical examinations, complete questionnaires, report the daily use of acetaminophen in a self-reporting notebook, report tolerance of the device and report adverse events (table 2). Adherence is evaluated by using a device tracker that provides information on its use with the daily time application and mean daily intensity since the previous visit. If necessary, patients undergo a new training session at weeks 4 and 8. The last visit at week 12 includes the same items of the follow-up visits plus a blood sample taken and a non-contrast MRI of the hand for the subgroup who had MRI at inclusion. Three specific additional assessments are added: asking about (1) satisfaction with the device; (2) ease of use of the device, rated on a 4-point scale; and (3) whether patients believed they had used the active or sham device. The investigators are asked whether they believe the patient has received the active or sham device.

Patients can withdraw from the study at any time for any reason. Patients will be withdrawn from the treatment if they comply with exclusion criteria but will continue to be monitored for the study.

### Randomisation

The investigator randomises patients to the active or sham tVNS groups by using the electronic case report form (e-CRF) CleanWeb (Telemedecine Technologies S.A.S.). The computer-generated, blocked, balanced randomisation is prepared in a 1:1 ratio by an independent biostatistician from the clinical research unit (URC-Est). The block width is not communicated to investigators. Randomisation is stratified by the centre. The investigator in charge of the randomisation is blinded to the randomisation group and selects the device according to the code number provided by CleanWeb and placed on the related device.

### Blinding

Active or sham devices look exactly the same. To homogenise between centres, the explanations given to the patients during the training session on the use of the device, a document with the verbatim to use for explanations was prepared by the coordinator and provided to the individuals in charge of training sessions in each centre. Manufacturing and preparation of the medical devices are handled by Schwa-Medico and are anonymised by the General Agency for Health Equipment and Products. Participants, investigators and all researchers involved in the data collection (investigators and nurses) or in biological and imaging analysis are blinded to the

**Table 2** Schedule of enrolment, interventions and assessments of the ESTIVAL study (Essai Randomisé Comparant Stimulation Auriculaire Transcutanée du nerf Vague versus Sham Stimulation dans l'Arthrose Digitale Érosive Symptomatique et Inflammatoire) according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines

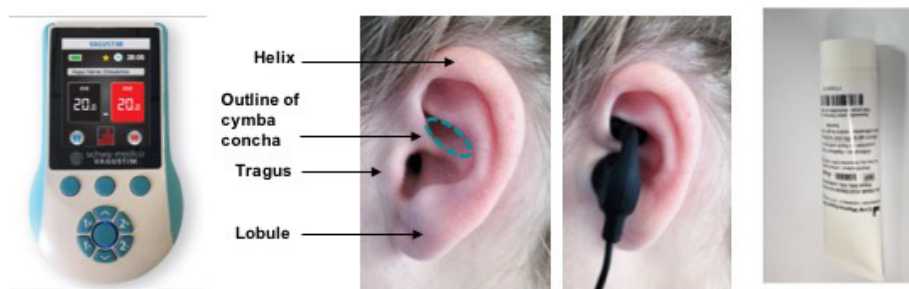
Timepoint	Study period				
	Screening Days 45–47	Allocation 0	Postallocation Week 4	Week 8	End of the study Week 12
<b>Enrolment</b>					
Eligibility screen	X	X			
Informed consent		X			
Hand radiography		X			
Hand joint ultrasonography		X			
Urinary $\beta$ -human chorionic gonadotropin test		X			
Electrocardiography		X			X
Randomisation		X			
<b>Interventions</b>					
Training session		X			
Active tVNS					
Sham stimulation					
<b>Assessments</b>					
Medical history	X				
Clinical general examination*		X	X	X	X
Hand clinical examination	X	X	X	X	X
VAS for hand pain in the last 48 hours	X	X	X	X	X
Morning stiffness		X	X	X	X
AUSCAN, FIHOA		X	X	X	X
Cochin Index		X			X
EQ-5D-5L		X			X
VAS for fatigue		X			X
HAD scale		X			X
DN-4 questionnaire		X			X
Knee/hip OA and WOMAC		X			X
Daily acetaminophen consumption (notebook)		X	X	X	X
PGIC					X
Patient and investigator beliefs					X
Device satisfaction/ease of use					X
Compliance			X	X	X
Adverse events			X	X	X
Blood samples		X			X
Hand MRI†		X			X

DN-4, a questionnaire about neuropathic pain.

\*Cardiopulmonary examination, blood pressure, search for orthostatic hypotension, heart rate, weight, height and left ear examination.

†Only a subset of patients undergo MRI of the most symptomatic hand at baseline and 12 weeks.

AUSCAN, Australian–Canadian Osteoarthritis Hand Index; DN-4, Douleur Neuropathique en Four Questions; EQ-5D-5L, EuroQol 5 Dimension 5 Level Quality of Life Questionnaire; FIHOA, Functional Index for Hand Osteoarthritis; HAD, Hospital Anxiety and Depression Scale; MRI, magnetic resonance imaging; OA, osteoarthritis; PGIC, Patient Global Impression of Changes Questionnaire; tVNS, transcutaneous vagus nerve stimulation; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.



**Figure 2** Description of the Vagustim device, the cymba concha, auricular electrode applied on the left cymba concha and the conductive gel provided to patients at the beginning of the study.

treatment allocation group until after the study completion and the analyses are fully performed at the end of the study. The investigator (outcome assessor) performs the clinical evaluation, and the clinical nurse or another medical doctor (different from the investigator) or the clinical study technician of each centre trains the patient in the device use. The investigating physician may request unblinding for any reason he considers essential to the health of the patient by contacting the project advisor. No unblinding is planned with the patient except in case of severe side effect.

During the follow-up visits, clinical efficacy is evaluated before recording potential minor stimulated site-treatment side effects. Because the clinical nurse or the person who performed the training session may guess the randomisation group according to the presence of these minor symptoms, no communication must occur between the investigator and the person who performed the training session and the patient during the study. We collect the initials of the person who performed the training session and the clinical assessor to ensure that they are different.

## Outcomes

### Primary outcome

The primary outcome is the difference between baseline and 12 weeks of self-reported hand pain in the previous 48 hours measured on a 100 mm VAS for the two groups. Patients are asked 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?’ and give the answer on a VAS.<sup>33</sup>

### Secondary outcomes

Secondary outcomes are the Australian–Canadian Osteoarthritis Hand Index (AUSCAN) subscores (pain, function and stiffness),<sup>34</sup> modified Functional Index for Hand Osteoarthritis (FIHOA) score,<sup>35</sup> Cochin Functional Index, EuroQoL EQ-D5 score,<sup>36</sup> Hospital Anxiety and Depression Scale score,<sup>37</sup> fatigue intensity (0–100 mm VAS), number of painful and swollen hand joints (0–30) on pressure, patient global assessment on a 0- to 100 mm VAS and the Douleur Neuropathique en Four Questions questionnaire

score evaluating the neuropathic pain component<sup>38</sup> and total consumption of acetaminophen (in grams).

As well, we evaluate response defined by the Patient Acceptable Symptom State for pain (VAS score <40/100),<sup>39</sup> the Outcome Measures in Rheumatology (OMERACT)-OARSI definition or according to the Patient Global Impression of Change (0, no change or very much worse, to 7, considerable improvement; patients with scores 5, 6 or 7 are considered ‘responders’ vs 1–4, non-responders).<sup>40 41</sup>

Finally, the number of side effects (such as auricular local irritation, contact allergy, subjective side effects can occur such as slight pain, unpleasant ‘prickling’, ‘tingling’, ‘itching’, ‘tickling’, etc) and the mean time of daily use and cumulative time of use of Vagustim during the 30 days before each visit collected from the device’s tracker are recorded as secondary outcomes.

### Exploratory outcomes

Blood samples of 8.5 mL are collected at baseline and 12 weeks to explore change in serum levels of inflammatory or pain-related markers (usCRP, interleukin (IL)-6, IL-8, TNF, nerve growth factor) and serum markers (cartilage degradation (cartilage oligomeric matrix protein), collagen 2–1 (Col2-1) level, a marker of type II collagen denaturation) and Col2-1–NO<sub>2</sub>, cartilage-based biomarkers<sup>42</sup> (more information in online supplemental file 2). Other serum biomarkers will be measured according to the state-of-the-art OA-related biomarkers at the end of the study.

A subset of patients will undergo non-contrast MRI of the hand. MRI of the target hand (ie, the most symptomatic hand at the baseline visit) is acquired by using whole-body 1.5 or 3.0 T MRI. The hand is meticulously and consistently aligned in the coronal and axial planes to ensure a similar orientation at measurements separated in time. The acquisition uses a field of view covering the IP joints. One reader reads the baseline and 12-week MRI images with known time sequence for each treatment period but blinded to treatment allocation. Synovitis and bone-marrow lesions are scored by using a modified OMERACT/Hand Osteoarthritis MRI Scoring Systems core as an exploratory outcome.<sup>43</sup>

If patients have symptomatic OA pain at the knee or hip, the Western Ontario and McMaster Universities Arthritis Index score is recorded at baseline and 12 weeks to compare the effect of tVNS versus sham on other OA joints.<sup>44</sup>

To assess the efficacy of the blinding procedure and the ease of use of the device, we evaluate the following at 12 weeks: the patient's satisfaction with treatment assessed on a 5-point scale (very satisfied to not at all satisfied), ease of use on a 4-point scale (very easy to very difficult), and the patients and investigator's beliefs about whether the patient had used the active or sham device.

### Statistical power

The study is powered to detect a difference between groups in change of at least 13mm at 12 weeks on a 100mm pain VAS scale. Considering an improvement in the sham group of  $11.3 \pm 24$ mm, a two-sided alpha risk of 0.05, a non-parametric test and a 10% drop-out rate with a power of 80%, and an additional margin of 20%, 156 patients are needed to randomise 130 of them<sup>45</sup> (East 6 (2020), statistical software for the design, simulation and monitoring clinical trials; Cytel, Cambridge, Massachusetts, USA). The choice of this 13mm cut-off is based on the expected important placebo effect in the sham group (effect size of the TENS placebo in knee OA is 0.44, 95% CI 0.14 to 0.74), the stable placebo effect on pain level at 3 and 6 months in HOA and known minimal clinically important changes in pain level in OA.<sup>45 46</sup> The additional margin of 20% in recruitment is justified because some patients will not have US-evidenced synovitis. From the study of Vlychou *et al*, among 22 patients with EHOA, 19 had a thickened synovium; 18 had power Doppler signals; and thus 4 of 22 (18%) had no US features of joint inflammation.<sup>10</sup>

### Data collection and management

Data are collected in an e-CRF, devised by the study coordinator in collaboration with URC-Est. Data are completed by the investigators with the help of a clinical research technician. Data entry checks and a posteriori checks are planned. All information required by the protocol are recorded in physical or electronic report files, and an explanation must be provided for any missing data. All questionnaires used are validated. A CRA will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the standard operating procedures applied within the clinical research and innovation department. A steering committee with a coordinator, coinvestigators and a methodologist decides what to do in unexpected situations. The committee monitors the progress of the research and meets every 12 months.

Source documents (original document or item that can prove the existence or accuracy of a data or a fact recorded during the study) are kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

During and after the research involving human participants, all data collected concerning the participants are rendered anonymous. Under no circumstances are the names and addresses of the participants shown. Only the participant's initials are recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research.

### Data analysis

Analysis will be performed at the end of the study after a blind data review and database lock. A flowchart will be drawn according to the CONSORT statement. Continuous variables will be summarised with mean $\pm$ SD or median (IQR), depending on the distribution of the variable. Categorical variables will be described with frequency (percentage). Primary analysis will be performed on the intent-to-treat (ITT) population defined as all patients randomised.

### Primary outcome

Difference in VAS pain (baseline minus week 12) will be compared between groups by using a Wilcoxon rank-sum test. The effect size and its 95% CI will be estimated. Additional analysis will be made to study VAS pain over time using a linear mixed model. In case of non-normal distribution, adapted transformation will be made.

Sensitivity analysis will be performed in the ITT population with available data and on the per protocol population defined as all patients randomised without major protocol deviation.

### Secondary outcomes

Change in AUSCAN subscores and modified FIHOA score will be compared by Student t-test or Wilcoxon rank-sum test (depending on data distribution). Other outcomes will be described in both groups and the difference between them calculated with the 95% CI. The slope over time in VAS pain score, FIHOA score and AUSCAN subscores will be described graphically by randomisation group, and a linear mixed model may be used to compare groups.

Missing data replacement strategy for the primary endpoint will be fixed according to the structure of the missing data structure. Other missing values will not be replaced. Statistical analysis will be performed with SAS V.9.4. All tests will be two-sided and a p value of  $<0.05$  will indicate statistical significance.

### Patient recruitment strategies

Recruitment of patients started in April 2021 and is expected for 2 years. In total, 18 French recruitment centres are involved: 17 rheumatology departments and 1 rehabilitation department in 18 hospitals (4 in Paris and 14 throughout France); 15 are academic hospitals (including 4 departments of Paris Assistance Publique des Hôpitaux de Paris (AP-HP) hospitals); 2 are regional

or departmental hospitals (Western region); and 1 is a private non-profit hospital (South of France, Marseille) for recruiting a wide range of patients with EHOA throughout France. However, because patients with EHOA are also often followed up in outpatient clinics, patients are also recruited from hospital consultations and by rheumatologists from private practice who work in collaboration with the investigator centres.

We used several communication channels to communicate about the study (French Society of Rheumatology and French Association for the Fight against Rheumatism (the largest patient's association devoted to musculoskeletal diseases in France)), the Arthritis Foundation, and publications in social network and the general media. We aimed also to contact the AP-HP network for communicating about ESTIVAL to the AP-HP patient community, which includes 39 hospitals. Flyers and posters are sent to the rheumatologists who participate to the OA study group of the French Society of Rheumatology. Finally, patients with EHOA can also contact us directly by letter or email. An ESTIVAL mailbox has been created for this purpose and is managed by the main investigator and/or the scientific director to refer patients to the nearest centre.

### Adverse events

Tolerance to the intervention was good in the pilot study and in studies in other indications with the only adverse event observed being an unpleasant sensation in the ear, mostly transitory, in a few patients.<sup>47</sup> However, information about adverse events and serious adverse events is collected throughout the study in the patient file and the eCRF. The investigator can temporarily or permanently withdraw a participant from the study or the patient may withdraw on their own for any safety reason or if it is in the participant's best interests.

### Patient and public involvement

There is no patient or public involvement.

### Ethics and dissemination

Ethics approval was obtained from the institutional review board at the main site (Comité de Protection des Personnes (CPP), 2020-A02213-36). All participants are required to provide written informed consent. Any substantial modification to the protocol by the coordinating investigator is sent to the sponsor for approval. After approval is given, the sponsor obtains approval from the CPP (research ethics committee) before the amendment can be implemented. The information note and the consent form can be revised if necessary, particularly in case of a substantial amendment to the study or if adverse reactions occur. Results of this study, whether positive or negative, will be presented at national and international congresses and published in a peer-reviewed journal.

## DISCUSSION

This is the first randomised study evaluating the tVNS in EHOA and in any OA joint. Here we chose a subset of patients with severe painful and inflammatory EHOA with clinical and US-confirmed synovitis to target the most severe and most symptomatic patients. We hypothesised that such a group will benefit most from tVNS because it targets pain as well as inflammation. We expect that tVNS will provide an analgesic effect over placebo in patients with EHOA and that it can be developed as a new non-pharmacological treatment in this subset of patients.

Recent randomised studies evaluating known synthetic or biological DMARDs failed to demonstrate efficacy in HOA or EHOA except for corticosteroids, which have a suspensive effect but also have safety concerns.<sup>14–18 48</sup> It is time to overcome the old scheme of already used rheumatic drugs and to develop innovative specific therapeutic targets in OA. Bioelectronic medicine is a new and promising field developed in several painful chronic conditions. Altered central sensitisation in patients with OA suggests altered CNS associated with chronic OA pain.<sup>49</sup> tVNS acts on CNS connectivity and plasticity involved in serotonergic and noradrenergic regulation, which may explain the analgesic effect in several contexts.<sup>50</sup> Moreover, tVNS also acts on inflammation, which is also involved in HOA-associated pain.<sup>51</sup>

We use here a non-invasive and usually very well-tolerated device. In a pilot study, the median decrease in hand pain on a VAS with tVNS applied with the same device was 23.5 mm (IQR 7.7–37.2) ( $p=0.001$ ) without any serious side effects. This encouraging study prompted us to conduct this randomised trial to determine the intrinsic efficacy of this device versus placebo with sham stimulation.

The design of the study follows the international guidelines for HOA clinical trials.<sup>33</sup> We considered previous data for calculating the sample size and considered possible limitations. Thus, the main issues in randomised trials evaluating tVNS are the quality and validity of the blinding.<sup>52</sup> Blinding of outcome assessors is essential, and we took additional measures, as recommended, to mitigate the potential bias from lack of blinding.<sup>53</sup> Concerning the sham procedure, some authors chose to perform stimulation at the same location (eg, cymba concha) but with low-frequency stimulation (1 Hz vs 25 Hz).<sup>54</sup> We did not choose this method because stimulation of the VN, although weak, cannot be excluded in this context. Other teams have preferred stimulation at another location (gastrocnemius or lobe of the ear), but then blinding is impossible for investigators, and we wanted to keep the blinding procedure as much as possible for the patient, nurse and investigator.<sup>55</sup> We decided on a sham stimulation at the same location (ie, cymba concha) to limit the possibility of unblinding patients and investigators. To appreciate the quality of the double-blinding, the final visit will include questions about whether the patients think they have had the active or the sham device. The same question will be asked of



the investigators concerning the active or sham device of the patient.

Regarding our primary and secondary outcomes, we expect that the tVNS treatment will decrease hand pain and improve hand function and quality of life in EHOA.

### Trial status

The recruitment started in April 2021 and will end in April 2023. The trial will end in July 2023, 3 months after the last inclusion.

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**Collaborators** ESTIVAL study group: Denis Arniaud; Jean-Philippe Bastard; Laurence Bérard; Francis Berenbaum; Julien Champey; Roland Chapurlat; Grégoire Cormier; Alice Courties; Camille Deprouw; Sandra Desouches; Florent Eymard; Soraya Fellahi; Jacques-Eric Gottenberg; Johanna Kalsch; Yves Henrion; Eric Lespessailles; Emmanuel Maheu; Hubert Marotte; Sylvain Mathieu; Anne Miquel; Paul Ornetti; Yves-Marie Pers; Nicolas Poursac; Francois Rannou; Anne-Christine Rat; Pascal Richette; Alexandra Rousseau; Christian H. Roux; Alain Sarau; Jérémie Sellam; Tabassome Simon; Amel Touati; Annick Tibi; Daniel Wendling.

**Contributors** AC, CD, AR, LB, AT, JK, MV, EM, AM, TS, FB and JS conceived and designed the study and participated in the implementation and data management of the study. AC and JS drafted the initial version of the manuscript. All the other authors provided critical revisions and approved the final revisions.

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### REFERENCES

- Haugen IK, Englund M, Aliabadi P, *et al*. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham osteoarthritis study. *Ann Rheum Dis* 2011;70:1581–6.
- Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. *Clin Rheumatol* 2002;21:231–43.
- Kwok WY, Kloppenburg M, Rosendaal FR, *et al*. Erosive hand osteoarthritis: its prevalence and clinical impact in the general population and symptomatic hand osteoarthritis. *Ann Rheum Dis* 2011;70:1238–42.
- Bijsterbosch J, Watt I, Meulenbelt I, *et al*. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. *Ann Rheum Dis* 2010;69:1784–8.
- Hodkinson B, Maheu E, Michon M, *et al*. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. *Ann Rheum Dis* 2012;71:145–9.
- Sellam J, Maheu E, Crema MD, *et al*. The DIGICOD cohort: A hospital-based observational prospective cohort of patients with hand osteoarthritis - methodology and baseline characteristics of the population. *Joint Bone Spine* 2021;88:105171.
- Patrick M, Aldridge S, Hamilton E, *et al*. A controlled study of hand function in nodal and erosive osteoarthritis. *Ann Rheum Dis* 1989;48:978–82.
- Wittoek R, Cruyssen BV, Verbruggen G. Predictors of functional impairment and pain in erosive osteoarthritis of the interphalangeal joints: comparison with controlled inflammatory arthritis. *Arthritis Rheum* 2012;64:1430–6.
- Haugen IK, Mathiessen A, Slatkowsky-Christensen B, *et al*. Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthritis a separate inflammatory phenotype? *Osteoarthritis Cartilage* 2016;24:647–54.
- Vlychou M, Koutroumpas A, Malizos K, *et al*. Ultrasonographic evidence of inflammation is frequent in hands of patients with erosive osteoarthritis. *Osteoarthritis Cartilage* 2009;17:1283–7.
- Wittoek R, Carron P, Verbruggen G. Structural and inflammatory sonographic findings in erosive and non-erosive osteoarthritis of the interphalangeal finger joints. *Ann Rheum Dis* 2010;69:2173–6.
- Punzi L, Ramonda R, Oliviero F, *et al*. Value of C reactive protein in the assessment of erosive osteoarthritis of the hand. *Ann Rheum Dis* 2005;64:955–7.
- Kingsbury SR, Tharmanathan P, Keding A, *et al*. Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis: a randomized trial. *Ann Intern Med* 2018;168:385–95.
- Davis CR, Ruediger CD, Dyer KA, *et al*. Colchicine is not effective for reducing osteoarthritic hand pain compared to placebo: a randomised, placebo-controlled trial (COLAH). *Osteoarthritis Cartilage* 2021;29:208–14.
- Chevalier X, Ravaud P, Maheu E, *et al*. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697–705.
- ACR Meeting Abstracts. Methotrexate in patients with hand erosive osteoarthritis refractory to usual treatments: a randomized, double-blind, placebo-controlled trial. Available: <https://acrabstracts.org/abstract/methotrexate-in-patients-with-hand-erosive-osteoarthritis->

- refractory-to-usual-treatments-a-randomized-double-blind-placebo-controlled-trial/ [Accessed 14 Apr 2020].
- 17 Richette P, Latourte A, Sellam J, et al. Efficacy of tocilizumab in patients with hand osteoarthritis: double blind, randomised, placebo-controlled, multicentre trial. *Ann Rheum Dis* 2020;annrheumdis-2020-218547.
  - 18 Kroon FPB, Kortekaas MC, Boonen A, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019;394:1993–2001.
  - 19 Wang H, Yu M, Ochani M, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 2003;421:384–8.
  - 20 Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 2000;405:458–62.
  - 21 Randich A, Gebhart GF. Vagal afferent modulation of nociception. *Brain Res Brain Res Rev* 1992;17:77–99.
  - 22 Rong P, Liu A, Zhang J, et al. An alternative therapy for drug-resistant epilepsy: transcutaneous auricular vagus nerve stimulation. *Chin Med J* 2014;127:300–4.
  - 23 Nemeroff CB, Mayberg HS, Krahl SE, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology* 2006;31:1345–55.
  - 24 Koopman FA, Chavan SS, Miljko S, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci U S A* 2016;113:8284–9.
  - 25 Bonaz B, Sinniger V, Hoffmann D, et al. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. *Neurogastroenterol Motil* 2016;28:948–53.
  - 26 Yakunina N, Kim SS, Nam E-C. Optimization of transcutaneous vagus nerve stimulation using functional MRI. *Neuromodulation* 2017;20:290–300.
  - 27 Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in musculoskeletal diseases. *Joint Bone Spine* 2021;88:105149.
  - 28 Courties A, Deproux C, Maheu E, et al. Effect of transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: results from a pilot trial. *J Clin Med* 2022;11:1087.
  - 29 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191–4.
  - 30 Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–94.
  - 31 Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601–10.
  - 32 Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39:308–20.
  - 33 Kloppenburg M, Maheu E, Kraus VB, et al. OARSI clinical trials recommendations: design and conduct of clinical trials for hand osteoarthritis. *Osteoarthritis Cartilage* 2015;23:772–86.
  - 34 Bellamy N, Campbell J, Haraoui B, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: development of the Australian/Canadian (AUSCAN) osteoarthritis hand index. *Osteoarthritis Cartilage* 2002;10:855–62.
  - 35 Dreiser RL, Maheu E, Guillou GB, et al. Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed* 1995;62:43S–53.
  - 36 EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
  - 37 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
  - 38 Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005;114:29–36.
  - 39 Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. *Arthritis Care Res* 2012;64:1699–707.
  - 40 Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976.
  - 41 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–21.
  - 42 Henrotin Y, Sanchez C, Bay-Jensen AC, et al. Osteoarthritis biomarkers derived from cartilage extracellular matrix: current status and future perspectives. *Ann Phys Rehabil Med* 2016;59:145–8.
  - 43 Haugen IK, Østergaard M, Eshed I, et al. Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. *J Rheumatol* 2014;41:386–91.
  - 44 Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833–40.
  - 45 Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. *Arthritis Rheum* 2011;63:3383–91.
  - 46 Zhang W, Robertson J, Jones AC, et al. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008;67:1716–23.
  - 47 Mertens A, Raedt R, Gadeyne S, et al. Recent advances in devices for vagus nerve stimulation. *Expert Rev Med Devices* 2018;15:527–39.
  - 48 Kloppenburg M, Ramonda R, Bobacz K, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018;77:1757–64.
  - 49 Loggia ML, Edwards RR. Brain structural alterations in chronic knee osteoarthritis: what can treatment effects teach us? *Pain Med* 2018;19:2099–100.
  - 50 Garcia RG, Lin RL, Lee J, et al. Modulation of brainstem activity and connectivity by respiratory-gated auricular vagal afferent nerve stimulation in migraine patients. *Pain* 2017;158:1461–72.
  - 51 Kortekaas MC, Kwok W-Y, Reijniers M, et al. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010;69:1367–9.
  - 52 Neugebauer EAM, Rath A, Antoine S-L, et al. Specific barriers to the conduct of randomised clinical trials on medical devices. *Trials* 2017;18:427.
  - 53 Boutron I, Moher D, Tugwell P, et al. A checklist to evaluate a report of a nonpharmacological trial (CLEAR NPT) was developed using consensus. *J Clin Epidemiol* 2005;58:1233–40.
  - 54 Bauer S, Baier H, Baumgartner C, et al. Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). *Brain Stimul* 2016;9:356–63.
  - 55 Addorasio ME, Imperato GH, de Vos AF, et al. Investigational treatment of rheumatoid arthritis with a vibrotactile device applied to the external ear. *Bioelectron Med* 2019;5:4.



**Full Research Title: Randomized Trial Comparing Transcutaneous Auricular Vagus Nerve Stimulation Versus Sham Stimulation in Symptomatic and Inflammatory Erosive Osteoarthritis: ESTIVAL**

**This research is promoted by the Assistance Publique - Hôpitaux de Paris  
Delegation for Clinical Research and Innovation  
1 avenue Claude Vellefaux  
75010 Paris**

## BRIEFING NOTE

**Madam, Sir,**

The Doctor/Professor (delete as appropriate) ..... (last name, first name), practicing at the hospital ..... proposes that you participate in a research project concerning your health condition.

It is important to read this note carefully before making your decision; do not hesitate to ask him for explanations.

If you decide to participate in this research, you will be asked for written consent.

### 1) What is the purpose of this research?

This research focuses on osteoarthritis of the hands (also called digital osteoarthritis). Osteoarthritis of the hands is one of the most common joint diseases and most often appears after the age of 40. It is a progressive destruction of the joints that causes pain and loss of mobility in the hand joints.

You have consulted a rheumatologist because you suffer from a particularly severe form of osteoarthritis of the hands, called erosive osteoarthritis of the hands (or erosive digital osteoarthritis). In erosive hand osteoarthritis, the pain is more intense and the functional discomfort is more severe.

That is why we are conducting a study to evaluate the effect of a potential new treatment on the symptoms of erosive hand osteoarthritis: the transcutaneous auricular vagus nerve stimulation.

To answer the research question, it is planned to include 156 people with erosive osteoarthritis of the hands, followed in several French rheumatology centres.

### 2) What does the research involve?

The purpose of the proposed research is to evaluate transcutaneous auricular neurostimulation of the vagus nerve in patients suffering from erosive hand osteoarthritis. It involves applying very low intensity electrical stimulation to the skin of the left ear using a small device called VAGUSTIM (transcutaneous electrical neurostimulation device). In this area of the ear, there is a nerve ending of a nerve, called the vagus nerve, whose stimulation leads to anti-inflammatory and pain-relieving (analgesic) effects.

There are already studies with this type of neurostimulation which have given positive results in other painful diseases such as migraine or fibromyalgia (diffuse pain), with a satisfactory tolerance profile. A study conducted at the Saint-Antoine Hospital in Paris on 20 patients all receiving this treatment gave encouraging results with a satisfactory safety and efficacy profile. We would like to demonstrate the effect of this neurostimulation in erosive hand osteoarthritis in a larger study.

In the proposed study, one patient out of two will receive the stimulation. The selection will be made by a computerised randomisation. Neither you nor the investigating physician will know the results of the randomisation until the end of the study.

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A neurostimulation kit (VAGUSTIM device, stimulation earpiece and electrical conduction gel) will be delivered to each patient. This kit will deliver or not the stimulation according to the allocated treatment: real or fake stimulation. This stimulation, real or fake, can sometimes be accompanied by a subjective itching or tingling sensation on the skin of the left ear, where the ear electrode is applied. Whether or not these sensations are experienced was observed in both treatment groups and did not affect efficacy or response to treatment.

In practice, it will consist of a neurostimulation session on the left ear 20 minutes per day at home (at any time of the day, in 1 session), for 12 weeks. We will teach you how to adjust and use the VAGUSTIM device, which is very easy to use. This device is already widely used in chronic pain (sciatica, acute lumbar back pain, neuropathy) and we will take the time to explain how it works.

### 3) What is the timeline for the research?

The expected duration of the research is 24 months and your participation will be for 12 weeks. After your consent is signed, at the first visit, the research will proceed as follows:

During the first visit, we will perform a clinical examination, an electrocardiogram (ECG), a blood test, an ultrasound of the hands and a hand X-ray. In some investigating centers (only in APHP centers), an MRI of the most painful hand will also be performed. You will be asked to fill out questionnaires about your hand osteoarthritis. If you are a woman of childbearing age, a urine pregnancy test will be performed. If you have no contraindication to participate in the study, the draw will be made and then we will teach you how to use the VAGUSTIM device and you will have the first neurostimulation session in the department, to check its correct use and its immediate tolerance. Then, you will use the VAGUSTIM device daily to perform the neurostimulation at home.

We will ask you to stop taking oral non-steroidal anti-inflammatory drugs (NSAIDs) or gel 48 hours before this first visit and for the duration of the study. The use of paracetamol (Doliprane, Efferalgan, Dafalgan) is possible during the study but we will ask you not to take it in the 48 hours preceding each visit.

At home, we will ask you to note your daily consumption of paracetamol in a booklet that we will give you and that you will have to return completed at the end of the study.

Two follow-up visits are scheduled at 4 and 8 weeks. During these visits, we will perform a new clinical examination and ask you to fill out the questionnaires related to your osteoarthritis again.

A final visit is scheduled at 12 weeks. This visit will be the same as the two previous ones, with the addition of a blood test and, in some centres (only APHP centres), an MRI of the hand. At the end of this visit, your participation in the study will be completed. We will collect the neurostimulation kit.

A c t i o n s	Selection visit (between D-45 and D-7)	Inclusion visit (D0 +/-7 days)	Visit Week 4 (S4 +/- 7 days)	Visit Week 8 (S8 +/- 7 j)	End of follow- up visit (S12 - 7 d/ + 10 d)
Information	X				
Written collection of informed consent		X			
Medical history	X				
Clinical Examination <sup>1</sup>	X	X	X	X	X
X-ray of the hands	X				
MRI of the hand (only for APHP centers)	X				X
Hand ultrasound		X			
Additional tests (heart exam, blood pressure, check for orthostatic hypotension, pulse, weight, height, left ear exam)		X	X	X	X
Pregnancy test		X			
<b>Randomisation</b>		X			

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ECG		X			
Blood test for biomarkers		X			X
– Use of the VAGUSTIM device and training session		X	X	X	
Compliance with treatment (extraction of daily session data from the device)			X	X	X
Adverse events			X	X	X

<sup>1</sup> Number of joints that are spontaneously painful and pressure sensitive, number of swollen joints (i.e.i.e. Synovitis), number of Heberden's and Bouchard's nodes (at D0 only), VAS pain at hand in the last 48 hours, duration of morning stiffness, DA questionnaires (AUSCAN, FIHOA, Cochin index), EuroQol EQ-D5D quality of life questionnaire, fatigue on VAS, anxiety depression questionnaire (HAD scale), DN-4 questionnaire (on D0 only), global health survey related to AD assessment, other symptomatic osteoarthritis location (c.-i.e. knee and/or hip), in case of knee and/or hip OA, pain assessment using VAS of the most painful hip and knee joint, WOMAC score, daily paracetamol consumption (at S4, S8 and S12).

#### 4) What are the benefits of your participation?

The expected benefit of participating in this study is a possible improvement in the symptoms of hand osteoarthritis, i.e. a reduction in hand pain and functional discomfort.

In addition, you will contribute to a better understanding of neurostimulation in erosive hand osteoarthritis.

By participating in this research, you will not be charged any additional fees.

#### 5) What treatments are allowed and not allowed?

Non-steroidal anti-inflammatory drugs (NSAIDs) applied topically to the fingers or orally and paracetamol should be discontinued at least 48 hours prior to first visit. No non-steroidal anti-inflammatory drugs (NSAIDs) should be taken during the entire study period.

Only paracetamol will be allowed during the 12 weeks of study participation and you will be asked to report your weekly paracetamol consumption during the 12 weeks of the study using a logbook.

Other analgesic drugs (strong opioids such as morphine or weak opioids such as tramadol or codeine) are not allowed during the 12 weeks of study participation.

Physiotherapy and orthotics are allowed if already prescribed and practiced before the beginning of the study.

#### 6) What are the foreseeable risks and constraints added by the research?

The risks associated with participation in this research are the minor adverse effects already reported with this type of device and auricular neurostimulation (local and transient irritation of the ear, slight pain, tingling, itching in the area of application of the electrode to the ear) which, in the majority of cases, have not led to the cessation of the use of the device in previous studies

If you agree to participate, you will have to respect the following points:

- Come to the follow-up appointments. If you are unable to attend, please contact your doctor as soon as possible.
- Inform the physician of the research, of the use of any medication and of any event occurring during the research (hospitalization, pregnancy, etc.).
- Bring back the documents specific to the research: paracetamol intake booklet (which will be given to you during the first visit).
- Do not take part in any other research project without your doctor's approval, in order to protect yourself from any possible accidents that could result, for example, from possible incompatibilities between the therapeutics studied or other dangers.
- Be affiliated to a social security scheme or be a beneficiary of such a scheme.

There is no financial compensation for your participation in this research. Transportation costs are not covered by the study.

#### 7) What will happen to the samples taken for research?

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Blood samples of 8.5ml will be taken at the inclusion visit and then at the end of the study (Week 12 - 7 days/ + 10 days) for all included patients, i.e. a total of 17ml for each patient which will be kept in a biological collection.

These samples will allow us to better understand the impact of vagal stimulation on the biological markers of cartilage degradation, pain and inflammation in digital osteoarthritis.

If not all the biological material is used for testing, it will be retained for further testing in the pathology.

With your agreement, the samples will be stored for 3 years at the Biological Resource Centre of the Saint Antoine Hospital (APHP, Paris). You may request their destruction at any time.

Some of these blood tubes will be sent to Belgium to the laboratory of Prof. Yves Henrotin (University of Liege, Artialis, Belgium). The shipment will be made anonymously.

### **8) What are the possible medical alternatives?**

If you do not participate in the research, you will continue to receive the usual care for osteoarthritis of the hands, and your non-participation will not affect this care.

### **9) What are the medical care arrangements at the end of your participation?**

At the end of the research, the neurostimulation kit will be retrieved and we will continue to manage you in accordance with the usual management of hand osteoarthritis.

Similarly, prematurely stopping the research leads to a return to your usual management of your hand osteoarthritis.

Your doctor may decide at any time to stop your participation; he or she will explain the reasons for this.

### **10) If you participate, how will the data collected for the research be handled?**

In the context of the research in which you are invited to participate, your personal data will be processed by the AP-HP, the research promoter and data controller, in order to analyse the results.

This processing is necessary to carry out the research that meets the public interest mission of the AP-HP as a public hospital-university health establishment

For this purpose, your medical and lifestyle data will be transmitted to the Promoter or to persons or partners acting on its behalf, in France. This data will be identified by a registration number. This data may also, under conditions that ensure their confidentiality, be transmitted to the French health authorities.

The medical data concerning you that can document a file with the competent authorities may be transmitted to an industrial company so that a greater number of patients can benefit from the results of the research. This transmission will be made under conditions ensuring their confidentiality.

Your data may be used for further research or analyses complementary to this research in collaboration with private or public partners, in France or abroad, under conditions that ensure their confidentiality and the same level of protection as the European legislation.

You may withdraw your consent for further use of your data at any time with the doctor who is treating you in this research.

Your data will only be kept for as long as is strictly necessary and proportionate to the purpose of the research. It will be kept in the information systems of the controller for up to two years after the last publication of the research results.

Your data will then be archived according to the regulations in force.

The computer file used for this research is implemented in accordance with French (amended Data Protection Act) and European (General Data Protection Regulation - GDPR) regulations. You have the right to access, rectify and oppose the processing of data covered by professional secrecy used in this research. These rights can be exercised with the doctor in charge of the research who alone knows your identity (identified on the first page of this document).

If you decide to stop participating in the research, the data collected prior to this stop will be used in accordance with the regulations, and exclusively for the purposes of this research. Indeed, their deletion would be likely to compromise the validity of the results of the research. In this case, your data will not be used at a later date or for any other research.

In the event of difficulties in exercising your rights, you can contact the Data Protection Officer of the AP-HP at the following address: [protection.donnees.dsi@aphp.fr](mailto:protection.donnees.dsi@aphp.fr), who will be able to explain to you the remedies available to you with the CNIL. You can also exercise your right to complain directly to the CNIL (for more information on this subject, visit [www.cnil.fr](http://www.cnil.fr)).

The following email address: [estival.aphp@gmail.com](mailto:estival.aphp@gmail.com) has been created so that patients interested in the ESTIVAL study can contact the medical team coordinating the project (Pr Sellam, rheumatology department, Saint Antoine hospital) if they have any questions about the study and wish to participate.

### 11) How is this research framed?

The AP-HP has taken all measures to conduct this research in accordance with the provisions of the Public Health Code applicable to research involving the human person.

The AP-HP has taken out an insurance policy (N°0100518814033 200122) guaranteeing its civil liability and that of all parties involved with the company HDI-GERLING through BIOMEDICINSURE whose address is Parc d'Innovation Bretagne Sud C.P.142 56038 Vannes Cedex.

The AP-HP has obtained a favorable opinion from the Comité de Protection des Personnes for this research [Ile de France V] on 06/10/2020.

### 12) What are your rights?

Your participation in this research is entirely free and voluntary. Your decision will not affect the quality of care and treatment you are entitled to expect.

During the course of the research, you can ask your doctor for information about your health and for explanations about the course of the research.

You can withdraw from the research at any time without justification, without any consequence on the continuation of your treatment or the quality of the care that will be provided to you and without any consequence on the relationship with your doctor. After this withdrawal, you may be followed by the same medical team. In this case, the data collected until the withdrawal will be used for the analysis of the results of the research.

Your medical file will remain confidential and can only be consulted under the responsibility of the doctor in charge of your treatment as well as by the health authorities and by persons duly mandated by the AP-HP for the research and subject to professional secrecy.

At the end of the research and after analysis of the data relating to this research, you can be informed of the overall results by asking the doctor who is following you in the context of this research.

You can also access all your medical data directly or through a doctor of your choice in application of the provisions of Article L 1111-7 of the Public Health Code.

After reading all this information, discussing all aspects with your doctor and after having had a period of reflection, 48 hours minimum, if you agree to participate in the research you will have to sign and date the informed consent form at the end of this document.



## CONSENT FORM

I, the undersigned, Mr <sup>me</sup>, Mr [*delete as appropriate*] (*surname, first name*)..... **freely agree to participate in the research entitled "Randomized trial comparing transcutaneous auricular stimulation of the vagus nerve versus sham stimulation in symptomatic and inflammatory osteoarthritis of the digestive tract: ESTIVAL"** organized by the Assistance Publique - Hôpitaux de Paris and proposed to me by the Doctor/Professor (*surname, first name, telephone*) ..... physician in this research.

- I have read the information note version 1.0 of 02/07/2020 [6 pages] explaining the purpose of this research, how it will be carried out and what my participation will involve,
- I will keep a copy of the information sheet and consent,
- I received appropriate answers to all my questions,  
I have had sufficient time to make my decision,
- I understand that my participation is free and that I may interrupt my participation at any time, without incurring any liability or prejudice to the quality of the care I receive.
- I have been informed that the data collected in the course of the research may be reused for further research, and that I may object to this at any time
- I am aware that my participation may also be interrupted by the doctor if necessary, and he/she will explain the reasons for this,
- I understand that in order to participate in this research I must be affiliated to a social security scheme or be a beneficiary of such a scheme. I confirm that this is the case,
- I have been informed that my participation in this research will last 3 months, and that this implies that I cannot consider participating in another research before the end of the study (at the end of the 12-week consultation), without informing the doctor who is following me in the research.
- My consent in no way relieves the doctor who follows me in the framework of the research nor the AP-HP of all their responsibilities and I retain all my rights guaranteed by law.

Signature of the person participating in the research		Physician's signature	
Last Name First Name :		Last Name First Name :	
Date:	Signature :	Date:	Signature :

### Specific consent for the biological collection

I agree to the collection and storage of blood samples, taken at the inclusion visit and at the end of the study, as part of my participation in the research and that these samples may be used to better understand the impact of vagal stimulation on biological markers of cartilage degradation, pain and inflammation in digital osteoarthritis. Biological material not used for analysis will be preserved for further analysis to better understand the disease.

### Signature of the person participating in the

### Research Physician's signature

Last Name First Name :

Last Name First Name:

Date:

Signature:

Date:

Signature :

Three copies of this document must be made, one copy must be kept for 15 years by the investigator, the second given to the person giving consent and the third sent to the AP-HP in a sealed envelope at the end of the research.

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## Biological specimens

Blood samples (baseline and 12w) collected at baseline and 12w, are centrifugated and serum is extracted, aliquoted (1mL) and frozen at -80° at each centre. Each taken sample will be anonymized with the reference number of the patient and the number of the visit. One baseline and one 12 w aliquots will be sent to Bone and Cartilage Research Unit, Université de Liège & Artialis, Liège, Belgium to perform serum markers of cartilage degradation (COMP, Coll2-1 and Coll2-1-NO2) and at service de Biochimie, Hôpital Henri Mondor AP-HP for serum inflammatory or pain-related markers (usCRP, IL-6, IL-8, TNF, NGF levels). Once analyzed, the results are sent at the end of the study to the data manager using a secured platform provided by AP-HP. The remaining aliquots are kept for 3 years.