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COPANOS: use of gabapentin in the management of post-viral parosmia – a double-blind, randomised, placebo-controlled, multi-site trial – study protocol

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ABSTRACT

Introduction Parosmia is a qualitative olfactory disorder characterised by a distorted perception of smell, often experienced as unpleasant or offensive. Although parosmia has multiple aetiologies, post-viral parosmia has become increasingly prevalent following the COVID-19 pandemic. In the UK, post-viral parosmia affects an estimated 637 836 individuals and has a substantial negative impact on quality of life and mood. At present, there is no licensed or standardised treatment for this condition. Gabapentin, a gamma-aminobutyric acid analogue with neuromodulatory properties, has shown potential benefits at low doses in small, non-randomised studies; however, its efficacy requires further evaluation.

Methods Use of Gabapentin in the Management of Post-Viral Parosmia: A Double-Blind, Randomised, Placebo-Controlled, Multi-Site Trial (COPANOS) is a phase III, double-blind, randomised, placebo-controlled trial comparing gabapentin with placebo in adults aged 18–65 years with post-viral parosmia persisting for ≥6 months and <5 years. Participants will be randomised 1:1 to receive gabapentin, titrated to a maximum dose of 600 mg daily or a matching placebo for 8 weeks. The primary outcome is the between-group difference in mean parosmia severity scores at the end of treatment (week 8), measured using the parosmia domain of the validated Smell-Qx questionnaire. Secondary outcomes include quality of life (Smell- Qx), olfactory function assessed using the Sniffin' Sticks test battery, safety and tolerability and objective parosmia severity measured with the Sniffin' Sticks Parosmia Test (SSParoT). The trial will recruit 90 participants across two UK sites.

Analysis The results will provide robust preliminary evidence on the efficacy and safety of low-dose gabapentin for managing post-viral parosmia and will inform the feasibility and design of targeted treatment guidelines. Defining effective treatment for post-viral parosmia is essential given the significant impact on patient well-being and the absence of current evidence-based interventions.

Ethics and dissemination The trial protocol has been reviewed and approved by Health Research Authority (HRA) and Health and Care Research Wales (HCRW): 25/WA/0298, 21/10/2025. Results will be analysed and published as soon as possible following trial completion. Findings will be summarised on the study webpage and shared with trial participants in plain English. Trial results will also be uploaded to relevant trial registries within 12 months of trial completion. The Rosetrees Trust will be acknowledged in all publications. Publications will follow International Committee of Medical Journal Editors authorship guidelines, and professional medical writers will not be used.

Trial registration number ISRCTN82171427, IRAS 1012783.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Double-blind placebo-controlled randomised controlled trial.
⇒ Patient-centred objective and subjective assessment using validated clinical tools
⇒ Thorough safety monitoring and evidence-based dosing regimen.
⇒ A limitation of this study is the absence of a third arm; no comparisons will be made between different neuromodulator medications or between high- and low-dose gabapentin.

INTRODUCTION

Background

Olfactory dysfunctions are broadly classified into quantitative and qualitative disorders. Quantitative disorders affect the detection and identification of odours, including conditions such as hyposmia and anosmia. In contrast, qualitative disorders alter the perception of odour quality and include parosmia, phantosmia and olfactory intolerance.[1 2]

Olfactory dysfunction has multiple aetiologies, including post-viral, post-traumatic, drug- or toxin-induced, secondary to

sinonasal pathology and idiopathic causes.[3] Among these, post-infectious olfactory dysfunction has become increasingly prevalent following the COVID-19 pandemic.[2 4–6] Parosmia is characterised as a qualitative olfactory dysfunction, where there is a distorted perception of smell in the presence of an odour. These distorted odours are typically described as unpleasant or offensive. Common descriptors include 'burned', 'foul', 'disgusting' and 'faecal'.[1 2] Persistent parosmia is estimated to affect 0.9% of the UK population, equating to approximately 637 836 individuals nationwide and is likely to significantly impact quality of life and mood.[5]

The pathophysiology of post-viral parosmia is not fully understood. Some evidence suggests that infections, such as COVID-19, may cause direct damage to olfactory receptor neurons, potentially leading to disorganisation or miswiring of olfactory sensory neurons.[6] Additionally, viral antigens have been observed to invade the central nervous system via the olfactory route, with the olfactory mucosa and bulb serving as potential entry sites. Previous MRI studies have shown that infections like COVID-19 can trigger cerebral abnormalities,[6] primarily affecting the limbic and olfactory cortical systems. Similarly, patients with parosmia have demonstrated specific loss of grey matter in anatomical regions such as the anterior insula, anterior insular complex and hippocampus—areas critical for odour discrimination and memory. Functional imaging has also revealed differential activation of central pathways in response to offensive odours.[2 3 6] These findings suggest that parosmia is likely driven by an interplay between central and peripheral mechanisms and there is a potential for neuromodulators in the treatment of parosmia.[7]

Current treatment landscape

There is currently no standard of care for treating patients with post-viral parosmia.[6] An international consensus statement on olfaction previously did not provide specific recommendations for the medical treatment of parosmia due to the high variation in treatment options and limited sample sizes.[6] Olfactory training, which involves smelling specific sets of odours twice daily for an extended period, has been shown to offer benefits for patients with post-infectious olfactory dysfunction, although it does not address parosmia directly. It is recommended in conjunction with other treatment options due to its low-risk potential. Medical treatments for parosmia have been evaluated in small cohort studies with variable success, including antipsychotics, antiseizure medications such as gabapentin and topical cocaine, but the results have been inconsistent.[2 6] Treatment options for parosmia remain limited, and there is currently insufficient high-quality evidence to support routine use of existing therapies. Small, non-randomised studies have suggested possible benefit from oral and intranasal corticosteroids.[2] Although there is insufficient data to support recommendations for intranasal/oral corticosteroids. Alpha-lipoic acid, a fatty acid with antioxidant and potential neuroregenerative properties, had shown some benefits, although not reaching significance or consistently replicated in subsequent studies.[2] Other approaches, including palmitoylethanolamide with luteolin, and vitamin A nasal drops, have also been investigated but have shown limited or no clear efficacy in post-infectious olfactory dysfunction or qualitative olfactory disorders such as parosmia.[8–10]

Rationale for gabapentin

Gabapentin has been explored in previous trials and exerts its effects by binding to voltage-gated calcium channels, which are crucial for neuronal synaptic transmission. Specifically, it inhibits the α2δ2 subunit, contributing to neuronal regeneration and function. Its lipophilic nature enables it to cross the blood-brain barrier, making it effective in treating central nervous system disorders such as neuropathic pain. Given its neuromodulatory properties and ability to penetrate the central nervous system, gabapentin is considered a promising treatment for post viral parosmia.[7 11]

The use of gamma-aminobutyric acid (GABA) analogues for managing parosmia has been previously reported in the literature and is not a new intervention.[7 11] Levy and Henkin reported lower brain GABA levels in patients with olfactory distortions,[12] with treatment aimed at normalising GABA levels being associated with clinical improvement.[7 12 13]

Garcia *et al* demonstrated an improvement in post-COVID-19 parosmia in 88.9% of patients following treatment with low-dose gabapentin using a titrated dosing schedule over 3 weeks.[7] However, this was a small study conducted on only nine patients. A more recent randomised controlled trial by Mahadev *et al* failed to demonstrate efficacy but employed high dosages with which adverse effects may have outweighed any potential clinical benefit.[11]

Other GABA analogues, such as pregabalin, list altered smell sensation as potential side effects and are therefore considered less appropriate for managing post-viral parosmia.[13 14] The dosage of gabapentin used in this trial is significantly lower than those used in studies related to chronic or neuropathic pain or the previous trial by Mahadev *et al* where dosages of 3600 mg were used.[11 15] This trial will aim for a maximum dose of 600 mg per day similar to that adopted by Garcia and colleagues.[7]

Rationale

Trial rationale

Persistent post-viral parosmia affects an estimated 637 836 individuals in the UK, and there is currently no licensed or standardised treatment or clinical guidance for its management.[5 6] This study aims to provide evidence to support the development of clinical guidelines in the management of parosmia.

The primary research question is whether gabapentin improves symptoms of post-viral parosmia compared with placebo in a double-blinded, randomised, controlled

trial. Existing treatments are off-label and supported only by small studies or using high doses of gabapentin with variable efficacy.[7 11]

The underlying premise is to identify a low-cost, widely available and effective treatment option for patients with post-viral parosmia, which is needed now more than ever in the wake of the COVID-19 pandemic. A randomised, placebo-controlled design has been chosen to ensure rigorous evaluation of efficacy and safety.

Participants will be eligible if they have experienced symptoms for 6 months to 5 years. The lower limit of 6 months was selected to reduce confounding from early spontaneous recovery in keeping with prior work which is common following post-infectious olfactory dysfunction.[8 16] The upper limit of 5 years was chosen to reflect the current clinical population with persistent post-infectious parosmia, most of whom are anticipated to have COVID-19-related or other post-viral smell dysfunction within this timeframe.

Dose rationale

Gabapentin is licensed in the UK at doses ranging from 300 mg to 3600 mg daily for indications including epilepsy and neuropathic pain.[17] Previous studies investigating gabapentin for parosmia have used variable dosing regimens. Garcia *et al* administered 200–600 mg daily, with only one participant reporting drowsiness.[7] In contrast, Mahadev *et al* titrated patients to a maximum daily dose of 3600 mg, with 10 of 14 participants reporting dizziness, although this was comparable to the control group.[11]

To optimise efficacy while minimising adverse effects, COPANOS will employ a maximum daily dose of 600 mg, with gradual titration over 4 weeks and a total treatment duration of 8 weeks. This regimen is consistent with prior studies and allows for slow dose escalation, which may improve tolerability. Gabapentin will be tapered to 300 mg once daily during weeks 7 and 8 before discontinuation to minimise the risk of withdrawal symptoms; notably, no withdrawal effects were reported following an 8 week treatment course by Mahadev and colleagues.[11]

Dose adjustment is not required for participants with a creatinine clearance >30 mL/min. Individuals with a creatinine clearance <30 mL/min, a history of renal failure, or those requiring dialysis will be excluded.[11 17] Adverse effects will be monitored via telephone consultations conducted between weeks 2 and 6, and participants will maintain diaries to document any adverse events.

The trial by Mahadev *et al* used high-dose gabapentin (up to 3600 mg/day), which is more likely to be associated with dose-dependent side effects. Doses exceeding 1800 mg/day have been linked to an increased incidence of sedation, dizziness, fatigue and ataxia, raising concerns regarding tolerability in a non-life-threatening condition such as parosmia. Clinicians are also likely to be reluctant to prescribe such high-dose gabapentin for olfactory dysfunction due to an unfavourable risk–benefit profile. Furthermore, the Columbia-Suicide Severity Rating Scale (C-SSRS)[18] will be employed to monitor for mood changes and suicidal ideation given advice that all antiepileptics may slightly increase risk of suicidal ideation.[17]

These considerations support the selection of a lower dose (600 mg/day), which is better tolerated, more aligned with real-world prescribing, and more likely to achieve clinical acceptability.

Objectives

Primary objective

To determine whether treatment with gabapentin for 8 weeks is effective in reducing parosmia severity (measured by Smell-Qx[19]) compared with placebo in adults with post-viral parosmia persisting ≥6 months but <5 years.

Null hypothesis

Treatment with gabapentin will lead to no difference in participant-reported outcome measures of parosmia compared with placebo following the treatment duration.

Alternative hypothesis

Treatment with gabapentin will result in improvement in patient-reported outcome measures of parosmia (parosmia domain of the Smell-Qx[19]) compared with placebo following the treatment duration.

Secondary objectives

i. To assess the impact of gabapentin on parosmia symptom severity, as measured by patient-reported outcome measures (parosmia domain of the Smell-Qx[19]), 4 weeks after completing treatment.
ii. To assess the safety and tolerability of gabapentin following the treatment duration.
iii. To assess the impact of gabapentin treatment on quality of life following the end of treatment (week 8).
iv. To compare the impact of gabapentin on olfactory function measured using the Sniffin Stick Smell Threshold-Discrimination-Identification (TDI) score.[20]
v. To assess the impact of gabapentin on objective parosmia symptom severity, as measured by the Sniffin' Sticks Parosmia Test (SSParoT).[21]

Exploratory objectives

i. To assess the impact of gabapentin on cognitive function.
ii. To assess the impact of gabapentin on nasal airflow.
iii. To assess the impact of gabapentin on taste function.
iv. To assess the impact of gabapentin on trigeminal sensitivity.
v. To assess the impact of gabapentin dosage on parosmia symptom severity at the end of treatment (week 8).

Trial design

Use of Gabapentin in the Management of Post-Viral Parosmia: A Double-Blind, Randomised, Placebo-Controlled, Multi-Site Trial (COPANOS) is a phase III, double-blind, randomised, placebo-controlled superiority trial. Enrolled participants will be randomised 1:1

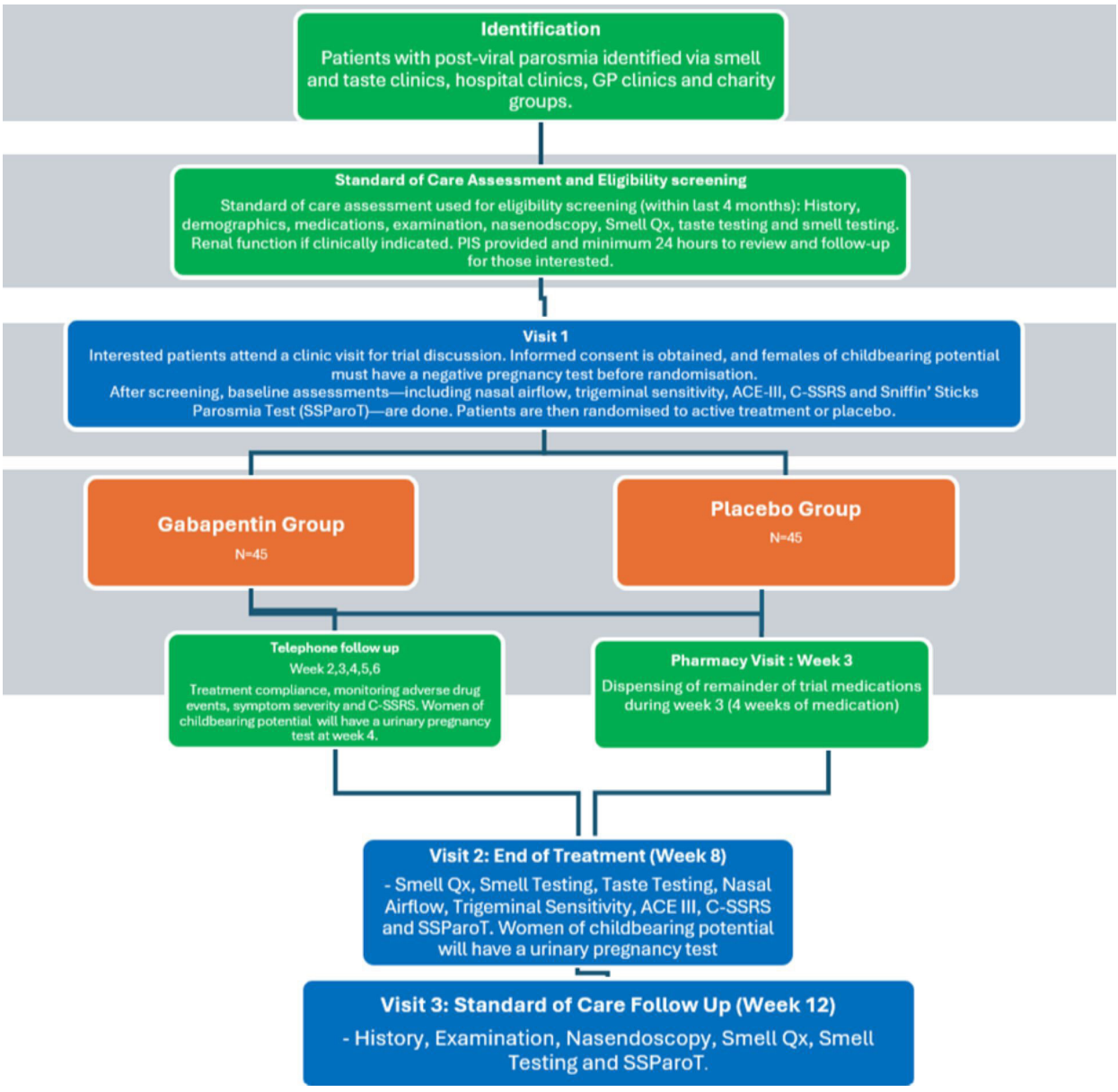

Figure 1 COPANOS trial schema. ACE-III, Addenbrooke's Cognitive Examination-III; C-SSRS, Columbia-Suicide Severity Rating Scale; GP, general practitioner; PIS, patient information sheet; SSParoT, Sniffin' Sticks Parosmia Test.

to receive gabapentin or matching placebo for 8 weeks. Treatment allocation will be blinded to participants and investigators. The trial schema is shown in figure 1. Recruitment is currently planned to commence in June 2026 and continue until March 2027, with timelines adjusted as required according to study set-up, recruitment progress, and operational considerations (Figure 2).

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

This is a multi-site trial conducted at two UK locations: Homerton Healthcare NHS Foundation Trust (primary site) and James Paget University Hospital NHS Foundation Trust (secondary site).

Recruitment

Participants will be recruited over 6–9 months through three pathways:

- **Smell & Taste Clinics:** Current patients identified through referral letters, existing records or routine attendance.
- **New referrals:** Via general practitioners (GPs), ENT specialists, respiratory clinics and Long COVID clinics.
- **Charitable organisations:** Via SmellTaste (formerly Fifth Sense) through social media, newsletters and mailshots.

Potential participants will be provided with the Participant Information Sheet and given at least 24 hours to consider participation before written informed consent is obtained.

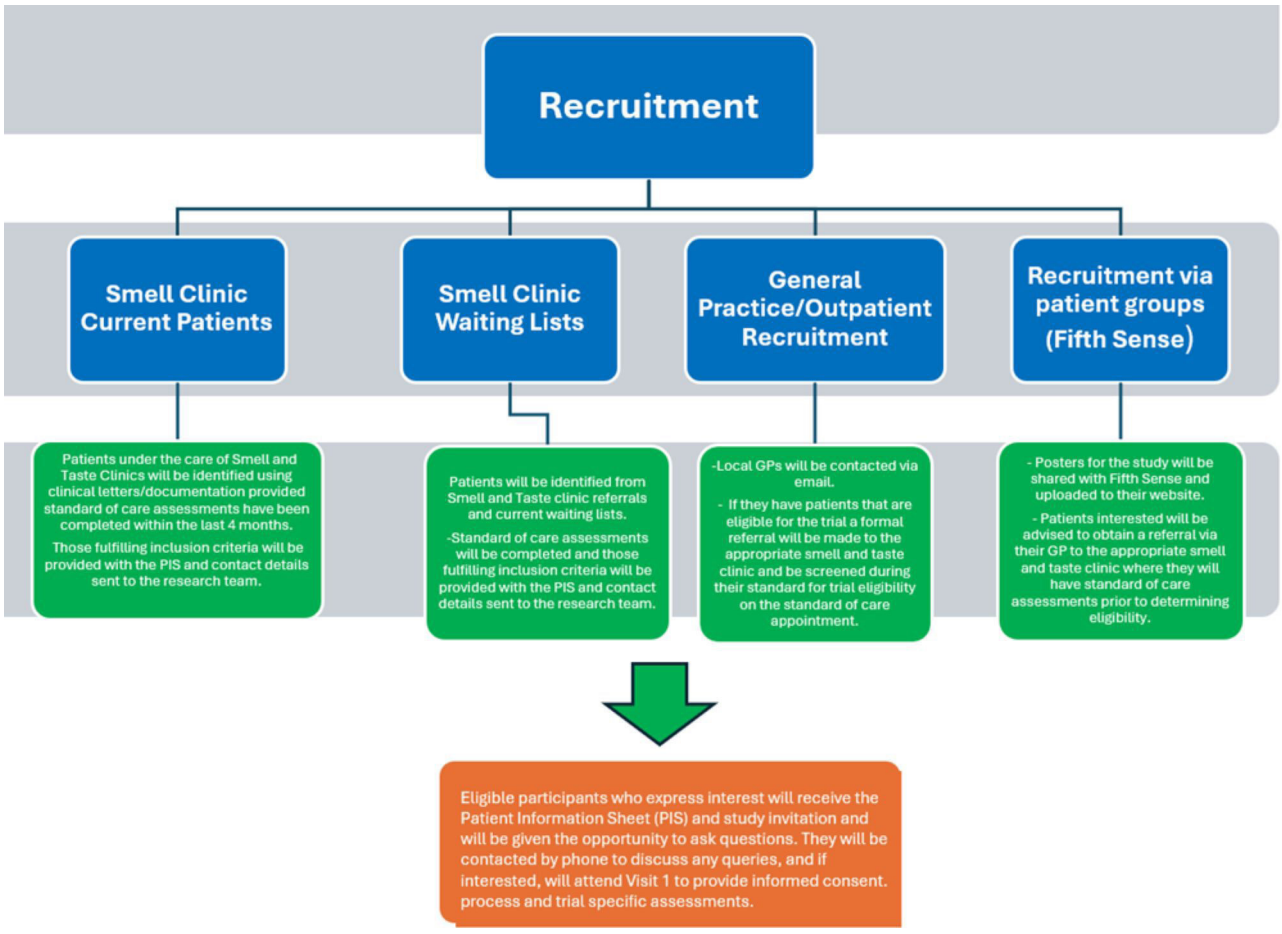

Figure 2 COPANOS trial recruitment. GPs, general practitioners.

Eligibility criteria

Inclusion criteria

- Adults aged 18–65 years with parosmia secondary to viral infection (≥6 months duration but <5 years).
- Parosmia domain severity score ≥3/5 on the Smell-Qx.
- Sniffin' Sticks TDI score >16.5 (excluding anosmia).
- Willing and able to provide written informed consent.
- Fluent in English and able to complete questionnaires.
- Women of childbearing potential must use highly effective contraception from consent until trial end.

Exclusion criteria

Key exclusion criteria include:

- Known allergy to gabapentin or its excipients.
- Parosmia primarily associated with chronic sinusitis, allergic rhinitis or sinonasal tumours.
- Use of antidepressants, antipsychotics or GABA analogues in the last 12 months.
- History of depression, anxiety, psychosis, self-harm or suicide attempts.
- History of neurological conditions (Alzheimer's, dementia, Parkinson's, epilepsy, traumatic brain injury).
- History of renal failure, dialysis or creatinine clearance <30 mL/min.
- History of liver failure or liver disease.
- History of cardiac arrhythmias or diagnosed heart failure.
- Pregnancy, planning pregnancy or breastfeeding.
- Current or previous addiction to alcohol, cocaine, opiates or other substances.
- Operating heavy machinery, working at heights or driving long distances professionally.

Interventions

Gabapentin arm

Participants will receive gabapentin 300 mg capsules with gradual titration over 8 weeks:

- Weeks 1–2: 300 mg once daily (evening).
- Weeks 3–6: 300 mg twice daily (600 mg total daily dose).
- Weeks 7–8: 300 mg once daily (weaning phase).

Placebo arm

Participants will receive matching placebo capsules following an identical dosing schedule.

Both gabapentin and placebo will be manufactured, over-encapsulated and packaged by a pharmaceutical partner to appear identical, ensuring blinding. All medications will be dispensed by site pharmacy in 4-week batches.

Dose modifications

If participants report tolerable side effects (eg, daytime drowsiness), they may reduce the dose to 300 mg once daily. Participants reporting subjective improvement by week 2 may remain on 300 mg daily rather than escalating to 600 mg. Participants experiencing allergic reactions or anaphylaxis will discontinue the trial medication and receive appropriate medical care.

Concomitant medications

Prohibited concomitant medications include all sedating medications and drugs that may interact with gabapentin, including alcohol, antidepressants, antipsychotics, antiepileptics, Parkinson's medications, opiates and other neuropathic agents. A complete list is provided in the trial protocol.

Outcomes measures

Primary outcome

The primary outcome is the difference in mean scores on the Parosmia domain of the Smell-Qx between gabapentin and placebo groups at the end of treatment (week 8). The Smell-Qx is a validated patient-reported outcome measure for smell and taste disorders.[19] The Parosmia domain uses a 5-point scale:

- 1=Very mild problem.
- 2=Mild or slight problem.
- 3=Moderate problem.
- 4=Severe problem.
- 5=Problem as bad as it can be.

A reduction in score indicates improvement in symptom severity (table 1).

Secondary outcomes

- Mean Parosmia domain scores (Smell-Qx) at 1-month post-treatment (week 12).
- Safety and tolerability: comparison of total number/percentage of patients with adverse drug reactions.
- Quality of life domain scores (Smell-Qx) at week 8 and week 12.
- Sniffin' Sticks TDI scores at week 8 and week 12.
- SSParoT scores (Hedonic Range and Hedonic Direction) at week 8 and week 12[21 22] (table 1).

Exploratory outcomes

Exploratory outcomes include cognitive function (Addenbrooke's Cognitive Examination-III), nasal airflow, taste function, trigeminal sensitivity and dosage impact on symptom severity (table 1).

Participant timeline

Visit 0 (standard of care pre-screening)

Patients undergo routine Smell & Taste Clinic assessments within 4 months prior to trial enrolment, including clinical history, nasal examination, flexible nasendoscopy (Lund-Kennedy Score will be documented), Sniffin' Sticks TDI test, Smell-Qx questionnaire and taste testing.

Visit 1 (baseline)

Informed consent, eligibility confirmation, pregnancy test (if applicable), baseline assessments (nasal airflow, trigeminal sensitivity, Addenbrooke's Cognitive Examination-III, SSParoT, C-SSRS), randomisation and first collection of intervention from pharmacy.

Weeks 2, 3, 4, 5, 6 (telephone follow-up)

Treatment compliance, adverse events (online supplemental table 1), C-SSRS and Smell-Qx Parosmia domain assessment. For women of childbearing potential, at-home pregnancy test at week 4.

Week 3 (pharmacy visit):

Collection of remaining intervention from pharmacy.

Table 1 COPANOS objectives and outcomes

Objective	Outcome measure	Instrument	Time point
Primary	Parosmia symptom severity	Smell-Qx Parosmia domain	Week 8
Secondary	Parosmia symptom severity (sustained effect)	Smell-Qx Parosmia domain	Week 12
	Safety and tolerability	Adverse events; C-SSRS	Weeks 0–8
	Quality of life	Smell-Qx QOL domain	Weeks 8, 12
	Olfactory function	Sniffin' Sticks TDI test	Weeks 8, 12
	Objective parosmia severity	SSParoT (HedRang, HedDir)	Weeks 8, 12
Exploratory	Cognitive function	ACE-III	Week 8
	Nasal airflow	Peak nasal inspiratory flow	Week 8
	Taste function	Taste strips test	Week 8
	Trigeminal sensitivity	Odour lateralisation test	Week 8
	Dosage impact on parosmia severity	Smell-Qx Parosmia domain (300 mg vs 600 mg)	Week 8

ACE-III, Addenbrooke's Cognitive Examination-III; AE, adverse event; C-SSRS, Columbia-Suicide Severity Rating Scale; HedDir, Hedonic direction; HedRang, Hedonic range; QOL, quality of life; SSParoT, Sniffin' Sticks Parosmia Test; TDI, threshold-discrimination-identification.

Visit 2 (week 8, end of treatment)

Repeat of all baseline assessments, adverse event review, pregnancy test (if applicable) and renal function testing if clinically indicated.

Visit 3 (week 12, 1-month post-treatment)

Final trial visit with standard of care and trial-specific assessments including clinical history, Smell-Qx, nasal examination, flexible nasendoscopy, Sniffin' Sticks TDI, taste testing, SSParoT and adverse events review.

Adherence will be assessed at each virtual follow-up visit by recording missed doses, current dose, treatment interruptions and tolerability. At the end of the treatment period, adherence will additionally be assessed through pill counts and return of empty medication bottles, with involvement from the trial pharmacist at each site. Intervention fidelity will be supported through standardised prescribing, dispensing, dose-escalation instructions and scheduled follow-up procedures to ensure that participants receive the allocated intervention according to the protocol.

Sample size

The sample size calculation was based on detecting a small treatment effect in Smell-Qx Parosmia domain scores between groups at week 8. Anticipating a more conservative treatment response than Mahadev *et al* who employed higher doses,[11] we assumed a small effect size defined as a probability of superiority P(X>Y)=0.324, where X represents control group scores and Y represents gabapentin group scores.

Sample size was calculated using the Wilcoxon–Mann–Whitney Sample Size Planning (WMWssp) R package with the following parameters: alpha (two-sided)=0.05, power=0.80, equal allocation ratio (1:1). This yielded a required sample size of n=70 (35 per group). To allow for an estimated 20% dropout rate, we increased the sample size to n=90 participants (45 per group).

Our estimated 20% dropout rate compared with the 36% rate reported by Mahadev and colleagues[11] is justified by our significantly lower gabapentin dose (600 mg vs 3600 mg daily). Garcia *et al* reported a 16.7% dropout rate,[7] further supporting this estimate.

RANDOMISATION

Sequence generation

Participants will be randomised in a 1:1 ratio to gabapentin or placebo using permuted-block sequencing. Randomisation will be stratified by baseline Parosmia domain scores ensuring balance between treatment groups.

Allocation concealment

Randomisation will be performed via Sealed Envelope, a centralised computer-generated randomisation system. The allocation sequence will be concealed from investigators and research teams. Authorised staff performing randomisation will be trained and listed on the site delegation log.

Implementation

On obtaining informed consent from eligible participants, a unique identification number will be assigned. Randomisation will occur after baseline assessments at week 0. The randomisation email will be sent directly to site pharmacy, which will dispense the trial medication according to the allocated treatment arm.

BLINDING

This is a double-blind trial. Neither participants nor the trial team will be aware of treatment allocation. Clinicians and trial team involved in the study assessments will be blinded from treatment allocation. Trial drugs will be identical in appearance and packing, prepared by a pharmaceutical partner using over-encapsulation. The blind will be maintained until all data entry is complete and the database is locked for analysis.

Unblinding will only occur for valid medical or safety reasons (eg, serious adverse events requiring knowledge of treatment allocation). The Chief Investigator or Principal Investigator will document code breaks with reasons in the Case Report Form, site file and medical notes, and notify the sponsor immediately.

DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection methods

Data will be collected using validated patient-reported outcome measures and objective assessments. All data will be recorded in electronic Case Report Forms by staff authorised on the site delegation log. Completeness will be optimised through telephone follow-up with participants who miss surveys or visits.

Data management

A trial-specific data management Standard Operating Procedure will detail software, database design, validation, data entry, quality checks, queries, security and database lock procedures. Data transfer will comply with UK Data Protection Act 2018 and UCL Information Security Policy.

Statistical methods

Primary analysis

The primary outcome will be analysed using an Analysis of Covariance (ANCOVA) model comparing mean Parosmia domain scores at week 8 between treatment groups, adjusting for baseline scores.

Sensitivity analysis

A mixed model for repeated measures (MMRM) will assess treatment effects over time, including baseline, week 8 and week 12 Parosmia domain scores. Fixed effects will include treatment group, timepoint, baseline score

and treatment×time interaction. This approach handles missing data under the Missing At Random assumption.

A per-protocol (PP) analysis will also be conducted as a sensitivity analysis. The PP population will include participants who complete treatment to week 8, have available primary outcome data and have no major protocol deviations expected to materially affect assessment of the primary outcome. Participants will be analysed according to the treatment received. The PP analysis will be used to assess the robustness of the primary analysis findings in participants who adhered sufficiently to the trial protocol.

Missing data

The primary ANCOVA analysis will use available data without imputation. If missing data exceed 10%, Multiple Imputation using chained equations will be considered. MMRM provides a principled approach to handling missing outcome data.

Secondary and exploratory analyses

Secondary outcomes will be analysed using appropriate parametric (t-tests, linear regression) or non-parametric methods (Mann-Whitney U test) based on data distribution. Categorical outcomes will use chi-squared or Fisher's exact tests. All tests will be two-sided with significance at $p<0.05$.

A PP analysis will be conducted as a sensitivity analysis, including participants who complete treatment (week 8) with available primary outcome data and no major protocol deviations.

All analyses will be performed using R (V.4.3.3 or later) and IBM SPSS Statistics (V.29 or later).

Data monitoring

An Independent Data Monitoring Committee (IDMC) will provide independent advice on data and safety aspects. Meetings will be held at least every 6 months. The IDMC is advisory to the Trial Steering Committee and can recommend premature trial closure.

Adverse event reporting

All adverse events will be recorded from consent until the final study visit (week 12). Serious adverse events must be reported to the sponsor within 24 hours. Severity will be assessed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V.5.0. Causality will be assessed by the investigator using clinical judgement. This will be documented in the adverse event table (online supplemental table 1).

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be assessed for expectedness against the Reference Safety Information (SmPC for Gabapentin 300 mg capsules, Tillomed Laboratories Ltd, Section 4.8). Fatal or life-threatening SUSARs must be notified to the The Medicines and Healthcare products Regulatory Agency (MHRA) within 7 days; other SUSARs within 15 days.

The Columbia-Suicide Severity Rating Scale (C-SSRS)[18] will be administered at baseline, during all telephone consultations (weeks 2–6), and at week 8. Participants reporting intermediate risk (C-SSRS items 2 or 3) will have their GP contacted and medication safely discontinued. High-risk participants (C-SSRS items 4 or 5) will receive immediate emergency care via 999. A significant mental health history is also in the exclusion criteria to further minimise this risk.

ETHICS AND DISSEMINATION

Research ethics approval

The trial protocol has been reviewed and approved by the Health Research Authority (HRA) and Health and Care Research Wales: 25/WA/0298, 21/10/2025. The protocol complies with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). Contact details for ethics committee: Wales.REC3@wales.nhs.uk.

Consent

Written informed consent will be obtained by Good Clinical Practice (GCP)-trained, appropriately qualified staff delegated by the Chief Investigator/Principal Investigator. Potential participants will receive the Participant Information Sheet at least 24 hours before consent. Participants will be clearly informed they are free to refuse participation or withdraw at any time without penalty or affecting their treatment.

Confidentiality

All data will be handled in accordance with the Data Protection Act 2018. Identifiable data will be collected at trial sites but will not leave the sites. Transferred data will be pseudonymised, containing only the participant's trial ID. The data custodian is the Chief Investigator or delegate.

Access to data

The final dataset will be available to the Trial Steering Committee. Site investigators may request access to the full dataset if a formal request is approved by the steering group and Chief Investigator.

Dissemination policy

Results will be analysed and published as soon as possible after trial completion. Findings will be summarised on the study webpage and provided to trial participants in plain English. The Rosetrees Trust will be acknowledged in all publications. Trial results will be uploaded to trial registries within 12 months of trial end. Publications will follow International Committee of Medical Journal Editors authorship guidelines. Professional medical writers will not be used.

Public and patient involvement

The team includes a public and patient involvement representative who has previous experience in clinical trial design and actively volunteers for SmellTaste, a charity supporting those with impaired smell or taste, having suffered anosmia for 10 years. They provided

valuable guidance on recruitment, information sharing and trial design. The PPI representative will be further consulted prior to dissemination of findings.

DISCUSSION

The COPANOS trial represents the largest phase III randomised controlled evaluation of gabapentin for post-viral parosmia, a condition currently lacking any licensed or standardised treatment.[2 6]

The trial design incorporates several important features to ensure trial safety and clinically robust results. The selection of an 8-week treatment duration with gradual dose titration to a maximum of 600 mg daily reflects a balance between therapeutic efficacy and safety, informed by previous trials that demonstrated tolerability concerns at higher doses.[11] The use of the validated Smell-Qx[19] as the primary outcome measure ensures patient-centred assessment of treatment efficacy, while the inclusion of objective measures such as the SSParoT[21 22] provides complementary objective data on parosmia severity. The Sniffin' Sticks TDI test serves as a validated measure of overall olfactory function.[20] Currently no Minimal Clinically Important Difference (MCID) exists for the Smell-Qx parosmia domain hence mean score differences will be used between groups for the primary outcome.[19] Furthermore, the treatment effects will be interpreted using the magnitude and precision of between-group differences, alongside SSParoT and other patient-reported quality-of-life outcomes, rather than against an arbitrary MCID threshold.

To mitigate the risk of confounding, we will record concomitant therapies at baseline and during follow-up, including whether participants are undertaking olfactory training, the nature of the regimen where available, and any changes during the trial. This data will allow us to describe the distribution of olfactory training use across trial arms and assess whether there is imbalance between groups and wider impact on outcomes.

Multisite involvement of two dedicated tertiary Smell & Taste Clinics, supplemented by recruitment through patient advocacy organisations such as SmellTaste, ensures both adequate recruitment rates and representation of patients across different healthcare settings. The trial's eligibility criteria carefully balance inclusion of patients who may benefit from treatment while excluding those at higher risk of adverse events, particularly through exclusion of patients with mental health histories and implementation of prospective monitoring using the C-SSRS.[18] The rationale for excluding those with a history of depression, anxiety, psychosis, self-harm or suicidal thoughts was twofold. First, gabapentin can influence mood and has been associated, although uncommonly, with neuropsychiatric adverse effects, including suicidal ideation. Therefore it is important to minimise risk in participants with pre-existing psychiatric vulnerability. Second, mood related symptoms could potentially influence patient-reported outcomes, particularly quality-of-life measures, and recent antidepressant use or medication changes could introduce additional confounding when interpreting treatment effects.

Importantly, the exclusion criterion does not preclude participation by individuals who have reduced quality of life related to smell or taste dysfunction but who do not have a formal psychiatric diagnosis or require antidepressant treatment. Mood and emotional impact are captured within the emotional domain of the Smell-Qx, including items assessing whether participants feel emotionally affected by their smell or taste problem, angry or annoyed, sad, worried, anxious or embarrassed.

If gabapentin proves effective in reducing parosmia severity, the trial results will provide robust evidence to guide clinical practice in this condition. A positive result would establish a safe, affordable and accessible treatment option for patients who currently have limited therapeutic choices. Gabapentin is already widely available across the UK and a positive result would support its use beyond current indications of neuropathic pain and epilepsy. Comprehensive safety monitoring will additionally provide valuable insights into the tolerability and optimal dosing of gabapentin in this population.

The COPANOS trial is managed by the Trial Management Group, comprising the Chief Investigator, trial staff and statistician, with day-to-day operations coordinated through regular meetings to review recruitment, safety data and protocol compliance. Independent oversight is provided by the Trial Steering Committee and the Independent Data Monitoring Committee, which will review accumulating trial data and provide recommendations regarding trial continuation, modification or early termination.

TRIAL STATUS

The trial is currently in the site setup phase. Regulatory and operational preparations are ongoing, and arrangements are being made for the distribution of the investigational medicinal product and placebo to site pharmacies prior to trial commencement.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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