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PHEnotyping type 2 inflammation in chronic rhinosinusitis with nasal polyps (CRSwNP) using RHeology of sinonasal secretions and tissue EOsinophil mapping in the middle turbinate

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Study protocol

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Abstract

Background

Chronic rhinosinusitis with nasal polyps (CRSwNP) is commonly driven by type 2 inflammation and frequently coexists with asthma, blood eosinophilia, elevated FeNO (fractional exhaled nitric oxide), and aeroallergen sensitization. Biologics targeting IgE, IL-5, and IL-4/IL-13 improve symptoms and polyp burden in severe CRSwNP, yet a substantial proportion of patients still require systemic corticosteroids or surgery, and clinically useful biomarkers for treatment selection remain limited. Local biomarkers may add value because systemic markers do not fully capture sinonasal inflammatory burden. Airway mucus rheology is an emerging biomarker in muco-obstructive lung disease, where viscoelastic properties correlate with eosinophilia and mucin content. In chronic rhinosinusitis, eosinophil extracellular traps and eosinophil-rich mucus are linked to disease severity and altered mucus physical. Rapid rheological assessment of native sinonasal secretions has not yet been established as a clinical biomarker in CRSwNP.

Methods

PheRhEos is a prospective, open-label, single-center, non-randomized comparative interventional study conducted at Montpellier University Hospital, France. Sixty adults undergoing endonasal surgery will be enrolled consecutively: 30 patients with CRSwNP and 30 control patients without inflammatory sinonasal disease. The primary objective is to compare the viscous modulus of sinonasal secretions between groups. Secondary objectives are to compare the elastic modulus and critical stress, tissue and blood eosinophilia, clinical severity, imaging, and respiratory variables, and to assess associations between local tissue inflammation, systemic type 2 biomarkers, and rheological properties. Sinonasal secretions will be collected by nose blowing and analyzed with the Rheomuco device. Middle turbinate tissue obtained during surgery will undergo histologic eosinophil quantification and immunostaining for eosinophil peroxidase and IL-5 receptor. Ancillary analyses include IL-5 and IL-13 blood measurements, tissue biomarkers, and proteomic profiling of secretions including mucins.

Discussion

Results will define whether rapid rheological profiling of sinonasal secretions can help phenotype CRSwNP and support future biomarker-driven studies of biologic selection and response.

Trial registration

ClinicalTrials.gov identifier: NCT07524127, registered 13 April 2026, prospectively registered before enrollment of the first participant.

Background

CRSwNP is a heterogeneous inflammatory airway disease associated with high symptom burden, repeated use of systemic corticosteroids, impaired quality of life, and frequent need for revision surgery. In Western populations, severe disease is commonly associated with type 2 inflammation, often with asthma and eosinophilic tissue infiltration (1–3). This has direct therapeutic implications because biologics targeting type 2 pathways have changed the treatment landscape. Dupilumab improved nasal polyp score, nasal congestion, CT opacification, and quality of life in the SINUS-24 and SINUS-52 phase 3 trials (4). Mepolizumab improved nasal polyp size and obstruction and reduced the need for surgery in SYNAPSE (5, 6). Omalizumab also improved endoscopic and patient-reported outcomes in the POLYP 1 and POLYP 2 trials (7).

Despite these advances, biologic response remains incomplete in a clinically relevant subset of patients. EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) and EUFOREA (European Forum for Research and Education in Allergy and Airways Diseases) therefore highlight the need for biomarkers that can better select patients, refine endotyping, and eventually guide biologic choice or switching (3). Current routine markers, including blood eosinophils, FeNO, total IgE, and allergy status, remain imperfect surrogates for local sinonasal inflammatory burden (8, 9). This matters because local eosinophilic activation appears closely linked to disease severity and refractoriness (10, 11).

Mucus is a plausible integrative biomarker because it reflects inflammatory cell activation, mucin composition, hydration, infection, and epithelial injury (12). In muco-obstructive lung diseases, sputum rheology correlates with eosinophilia, MUC5AC, MUC5B, and total protein, supporting a clinically useful bridge between biophysics and inflammatory phenotyping (13, 14). In chronic rhinosinusitis, eosinophil-rich mucus has higher viscosity, greater dry weight, and altered wettability, and eosinophil-specific proteins correlate with these physical properties (15). Eosinophil extracellular traps are also strongly associated with tissue eosinophils, blood eosinophilia, CT severity, and olfactory dysfunction (11), while EETosis is associated with postoperative refractoriness (10). Together, these findings support the hypothesis that rheological profiling of sinonasal secretions may capture clinically relevant local type 2 inflammation.

PheRhEos was designed to test two linked hypotheses. First, sinonasal secretions from patients with CRSwNP differ rheologically from those of surgical controls without inflammatory sinonasal disease. Second, these rheological properties are associated with local eosinophilic inflammation and may therefore complement systemic biomarkers in CRSwNP phenotyping. A further aim is to characterize eosinophil distribution within the middle turbinate, because heterogeneous tissue infiltration may affect the diagnostic yield of routine biopsy sampling.

Methods/Design

Study design and setting

PheRhEos is a monocentric, prospective, open-label, non-randomized comparative interventional study conducted at Montpellier University Hospital, France. Participants will be enrolled consecutively into one of two groups: 1) CRSwNP group: adults with CRSwNP and an indication for sinonasal surgery 2) Control group: adults without CRSwNP undergoing endonasal surgery for a non-inflammatory indication such as septoplasty, turbinoplasty, posterior nasal cryotherapy, endonasal orbital decompression, or pituitary surgery. No randomization or matching is planned.

Participants

Eligbility criteria

Participants were eligible if they were 18 to 85 years of age, had an indication for endonasal surgery, and were able to read and write, complete the study procedures, and provide written informed consent. For inclusion in the CRSwNP group, participants were additionally required to have bilateral nasal polyps meeting EPOS 2020 diagnostic criteria (2), defined by symptoms lasting at least 12 weeks, at least two sinonasal symptoms, including nasal obstruction or rhinorrhea, and bilateral polyps visible on endoscopic examination. Control participants were required to have no CRSwNP or other inflammatory sinonasal disease and to be undergoing endonasal surgery for a non-inflammatory indication. Participants were not eligible if they had a contraindication to endonasal surgery, secondary nasal polyposis, including cystic fibrosis, primary ciliary dyskinesia, immune-mediated disease, or allergic fungal rhinosinusitis, lacked informed consent or social-security coverage, were under legal protection, or were participating in another research study with an active exclusion period.

Recruitment, Ethics and Consent

Potential participants will be informed about the study during routine otorhinolaryngology consultation. Eligibility will be checked by the investigator. Written informed consent will be obtained before any research-specific procedure. Participation is voluntary, and participants may withdraw consent at any time without affecting their care. This study was approved by the local Institutional Review Board (CHU de Montpellier IDRCB: RECHMPL24_0379–2025-A01490-49) and registered on ClinicalTrials.gov on April 13, 2026, NCT07524127. It will be conducted in accordance with the Declaration of Helsinski.

Study visits and procedures

The study includes an inclusion visit and a surgical visit.

At the inclusion visit, eligibility will be confirmed, consent obtained, demographic data recorded, clinical examination and nasal endoscopy performed, and questionnaires completed. If feasible, sinonasal secretions may be collected at this visit. Surgery will be scheduled approximately 1 month later, within a window of plus or minus 30 days.

During the preoperative interval, participants will undergo standard-of-care assessment for surgery. This includes sinus CT (computed tomography). Chest CT, spirometry, and FeNO may be performed when clinically indicated, particularly in patients with suspected asthma.

At the surgical visit, blood sampling will be performed, sinonasal secretions will be collected if not already obtained at inclusion, and middle turbinate tissue will be obtained intraoperatively for histology and immunostaining. No study-specific follow-up visit is planned after surgery and sample collection. Study visits and procedures are described in Table 1.

Table 1
Study visits and procedures

Assessment	Inclusion visit	Preoperative interval	Surgical visit
Eligibility and consent	X		
Demographic and clinical data	X		X if required
Nasal endoscopy	X		
Questionnaires	X		
Sinus CT		X	
Chest CT, spirometry, and FeNO if clinically indicated		X	
Sinonasal secretion collection	X or surgical visit		X if not already performed
Blood sampling			X
Endonasal surgery			X
Middle turbinate histology and immunostaining			X
Rheological analysis	After secretion collection		After secretion collection

Collection and rheological analysis of sinonasal secretions

Sinonasal secretions will be collected by nose blowing onto an aluminum plate, adapted from prior methods for undiluted nasal secretion sampling (16). Both nostrils will be sampled. The specimen will be transferred to an Eppendorf tube without dilution. Rheological analysis will be performed on at least 400 µL of fresh secretion after low-speed vortex homogenization for 1 minute. If analysis within 1 hour is not feasible, the specimen will be stored at − 80°C for later analysis. Rheology will be measured with the Rheomuco rheometer at 37°C, using an oscillation frequency of 1 Hz and increasing strain, following the analytical approach previously used in airway secretions (14). The following variables will be recorded: 1)

viscous modulus G″, Pa; 2) elastic modulus G′, Pa; 3) critical stress σc. After rheological testing, the same specimen will be sent for direct bacteriological examination and culture.

Tissue sampling and histology

Middle turbinate tissue will be obtained during surgery. When resection of the middle turbinate is part of standard care, serial axial sections will be prepared every 3 mm after hematoxylin-eosin staining. Eosinophils will be quantified in the medial surface, lateral surface, anterior border, and posterior portion of the middle turbinate in order to assess spatial heterogeneity. When resection is not part of standard care, a targeted biopsy of the middle turbinate head will be performed according to the same histologic workflow. Immunostaining for eosinophil peroxidase and IL-5 receptor will also be performed.

Clinical and paraclinical variables

The following variables will be collected:

1) Nasal endoscopy variables, including Nasal Polyp Score, septal deviation, inferior turbinate hypertrophy, secretion appearance, and mucosal appearance.

2) Patient-reported outcomes: SNOT-22, DyNaChron, and CRS-PRO (French validated version (17)); in participants with asthma, Asthma Control Questionnaire and St George's Respiratory Questionnaire.

3) Medication exposure, with specific attention to intranasal corticosteroids, short- and long-acting bronchodilators, inhaled corticosteroids, oral corticosteroids, azithromycin, and other antibiotics.

4) Blood eosinophil count and albuminemia.

5) FeNO, spirometry, sinus CT and chest CT when available from standard care.

The standard systemic type 2 profile will be defined by at least one of the following: blood eosinophils greater than 150 cells/mm³ or greater than 2%, FeNO at least 20 ppb, or sensitization to aeroallergens (3).

Outcomes

The primary outcome is the between-group difference in sinonasal secretion viscosity, defined by the viscous modulus G″.

Secondary and exploratory outcomes are summarized in Table 2.

Table 2
Study Outcomes

Domain	Outcome	Timing	Classification
Rheology	Viscous modulus G″	Preoperative secretion sample	Primary
Rheology	Elastic modulus G′; critical stress σc	Preoperative secretion sample	Secondary
Tissue inflammation	Tissue eosinophil quantification	Surgical sample	Secondary
Systemic inflammation	Blood eosinophilia; FeNO	Preoperative assessment	Secondary
Clinical phenotype	Clinical characteristics; endoscopic severity; questionnaires	Inclusion and preoperative assessment	Secondary
Imaging and lung function	Sinus CT; Chest CT; spirometry	Standard-care availability	Secondary
Biomarker associations	Associations between local tissue inflammation, systemic inflammation, and rheology	Cross-sectional	Secondary
Microbiology	Correlation between microorganisms in nasal secretions and rheology	Same sample as rheology	Secondary
Ancillary biomarkers	EPX, IL-5 receptor, TSLP receptor, IL-5, IL-13, proteomics including MUC5AC and MUC5B	Stored tissue and blood or secretion samples	Exploratory

Sample size

The sample size is based on detecting a 1.5-point difference in G″ between groups, assuming a common standard deviation of 2 points, 80% power, and a two-sided alpha of 0.05. This requires 28 analyzable participants per group. To account for non-analyzable data, 60 participants will be included, with 30 per group.

Statistical analysis

All included participants will be analyzed. Quantitative variables will be summarized as mean and standard deviation when normally distributed and as median and interquartile range otherwise. Qualitative variables will be summarized as counts and percentages. Distributional assumptions will be explored using the Shapiro-Wilk test.

The primary outcome will be compared between groups using a parametric or non-parametric test according to distribution. Secondary quantitative outcomes will be analyzed similarly. Categorical variables will be compared using chi-square or Fisher exact tests, as appropriate. Associations between

rheological variables and tissue or systemic inflammatory markers will be assessed by correlation analyses. A detailed statistical analysis plan will be finalized before database lock.

Analyses involving FeNO, spirometry, and chest CT will be exploratory because these variables are available only when clinically indicated.

Biological collection and ancillary analyses

The study includes a blood biobank and a biobank of sinonasal secretions stored at − 80°C under coded identifiers for up to 2 years. Participants may refuse biological storage while remaining in the main study. Planned ancillary analyses include: 1) proteomic analysis of sinonasal secretions by mass spectrometry, including MUC5AC and MUC5B; 2) blood measurements of IL-5 and IL-13; 3) tissue analyses of eosinophil peroxidase, IL-5 receptor, and TSLP receptor.

Safety

The study adds minimal risk to standard surgical care. The main research-specific risk is the additional blood draw, which may cause local hematoma. No specific risk is expected from collection of sinonasal secretions by nose blowing. No participant compensation is planned, and no exclusion period for participation in another study is created by this protocol.

Participants may withdraw consent at any time. The investigator may also discontinue participation early in the event of consent withdrawal, intercurrent illness, or another decision made in the participant's interest. The reason for early discontinuation will be documented in the medical record and case report form.

Declaration of generative AI and AI-assisted technologies

During the preparation of this work, AI-assisted language (Claude) was used to assist in English Proofreading. The authors reviewed and edited the content as needed and take full responsibility for the content of the submitted manuscript.

Discussion

PheRhEos addresses a practical gap between the growing use of biologics in CRSwNP and the limited availability of biomarkers that reflect local disease biology. Current treatment decisions rely largely on severity, prior surgery, systemic corticosteroid exposure, smell loss, asthma, and broad type 2 markers (3). Yet several studies suggest that local inflammatory burden is not fully captured by systemic markers alone. Local IL-5 and tissue eosinophilia can distinguish high- and low-inflammatory subgroups even within patients already considered likely to have type 2 disease (8). Eosinophil extracellular traps correlate with CT severity, olfactory dysfunction, blood eosinophilia, and postoperative refractoriness. These findings support a local biomarker strategy.

The present protocol is clinically pragmatic. Secretion sampling is non-invasive, rapid, and compatible with routine care. If rheological variables discriminate CRSwNP from non-inflammatory surgical controls and correlate with eosinophilic inflammation, sinonasal rheology could become a point-of-care biomarker analogous to the translational role proposed in lower airway disease (14). The protocol also adds a histologic mapping component in the middle turbinate, a site commonly sampled in practice but insufficiently characterized as a spatial biomarker source.

This study has limitations. It is single-center and modest in size. The control group is composed of surgical controls rather than healthy volunteers, which improves procedural comparability but may reduce biological contrast. Some respiratory variables are available only in participants investigated for suspected asthma, which introduces structured missingness. Finally, the study is powered for a cross-sectional rheological comparison rather than for prediction of biologic response. A positive signal would nevertheless justify larger validation studies and future longitudinal work in patients treated with biologics.

In summary, PheRhEos will test whether rapid rheological analysis of sinonasal secretions, integrated with tissue eosinophil mapping and systemic biomarkers, can refine phenotyping in CRSwNP. If successful, it may support the development of a practical biomarker strategy for personalized management of upper airway type 2 disease.

Abbreviations

ANR
Agence nationale de la recherche
CHU
Centre hospitalier universitaire
CRS
Chronic rhinosinusitis
CRS-PRO
Chronic Rhinosinusitis Patient-Reported Outcome (pmc.ncbi.nlm.nih.gov)
CRSwNP
Chronic rhinosinusitis with nasal polyps
CT
Computed tomography
DyNaChron
Dysfonctionnement Nasal Chronique questionnaire, or chronic nasal dysfunction questionnaire
EETosis
Eosinophil extracellular trap formation
EPOS
European Position Paper on Rhinosinusitis and Nasal Polyps
EPX

Eosinophil peroxidase
EUFOREA
European Forum for Research and Education in Allergy and Airways Diseases
FeNO
Fractional exhaled nitric oxide
IgE
Immunoglobulin E
IL-4
Interleukin-4
IL-5
Interleukin-5
IL-13
Interleukin-13
MUC5AC
Mucin 5AC
MUC5B
Mucin 5B
SNOT-22
22-item Sino-Nasal Outcome Test
TSLP
Thymic stromal lymphopoietin

Declarations

Ethics approval and consent to participate

Written informed consent will be obtained before any research-specific procedure. Participation is voluntary, and participants may withdraw consent at any time without affecting their care. This study was approved by the local Institutional Review Board (CHU de Montpellier IDRCB: RECHMPL24_0379–2025-A01490-49) and registered on ClinicalTrials.gov on April 13, 2026, NCT07524127. It will be conducted in accordance with the Declaration of Helsinski.

Consent for publication

Not applicable

Competing interests

The authors declare no conflict of interest in relation with this manuscript.

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Author Contribution

A.P. and I.V. will perform the cytology, protein assays and rheological analysis of the samples. V.F., J.C., and A.B. participated in the design of the study. E.A and Z.M.L. will collect clinical data. N.M. will perform the statistical analyses. All the authors equally contributed to the writing of the manuscript and its review.

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Availability of data and materials

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request.

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