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BMJ Open Study protocol: the biologics in severe chronic rhinosinusitis with nasal polyps survey

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ABSTRACT

Introduction Chronic rhinosinusitis with nasal polyps (CRSwNP) is a frequent condition affecting approximately 2% of the population. Medical treatment consists long-term use of intranasal corticosteroids and short-term use of oral corticosteroids, in adjunct with saline solution rinses. Surgical management is proposed in patients who failed after medical treatment. In France, two biologics are reimbursed in case of severe uncontrolled CRSwNP despite medical treatment and endoscopic sinus surgery. Waiting for head-to-head biologics comparison, studies should report the efficacy and safety of biologics in large real-life cohorts. This study protocol describes the aims and methods of a prospective, observational, national, multicentric cohort of patients with CRSwNP treated with biologics.

Methods and analysis The BIOlogics in severe nasal POLyposis SurvEy is a French multicentre prospective observational cohort study. The main aim is to assess the efficacy and tolerance of biologics in patients with CRSwNP, with or without association with other type 2 diseases, and to determine the strategies in case of uncontrolled disease under biologics. Patients over 18 years old requiring biologics for CRSwNP in accordance with its marketing approval in France (ie, severe nasal polyposis, with lack of control under nasal corticosteroid, systemic corticosteroids and surgery) are invited to participate. Collected data include topical history of surgical procedures and biologics, medication and use of systemic corticosteroids, visual analogical scales for specific symptoms, Sino-Nasal Outcome Test-22 questionnaire, nasal polyp score, asthma control test, Lund-Mackay score on CT scan and IgE concentration and eosinophilic count on blood sample.

Trial registration [NCT05228041](https://clinicaltrials.gov/ct2/show/study/NCT05228041)/DRI_2021/0030.

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a frequent condition affecting approximately 2% of the population.^{1–5} In most cases, a type 2 inflammation is responsible for changes of the sinonasal mucosa

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The BIOlogics in severe nasal POLyposis SurvEy is a multicentre French prospective observational clinical cohort study.
- ⇒ The cohort is representative of patients with chronic rhinosinusitis with nasal polyps (CRSwNP).
- ⇒ Nasal function, patient-reported information on nasal symptoms and health-related quality of life are all collected with disease-specific tools, in a standardised way.
- ⇒ Biologics received are not randomised at inclusion; therefore, a direct comparison of the different treatments will not be possible.
- ⇒ This cohort study enables a real-life assessment of dupilumab and mepolizumab, prescribed for recurrent CRSwNP after a previous surgery.

leading to oedema and polyp formation. Patients complain of nasal obstruction, olfactory loss, rhinorrhea and facial pain.⁶ CRSwNP also has an impact on sleep and mental health quality of life (QoL),^{7 8} resulting in high symptom burden. Type 2 CRSwNP inflammation and symptoms can be controlled using the long-term use of intranasal corticosteroids and the short-term use of oral corticosteroids, in adjunct with saline solution rinses.^{1 9} Endoscopic sinus surgery could be proposed in an uncontrolled patient despite appropriate use of local and systemic corticosteroids.^{1 10 11} Outcomes of endoscopic sinus surgery are variable according to population and techniques used.^{12–20} In some patient, this standard of care medical and surgical strategy fails to control symptoms and QoL.²¹

The identification of type 2 CRSwNP endotypes has permitted to specifically target this inflammation pathway using biologics. Type 2 CRSwNP shares pathophysiology mechanisms with hypereosinophilic asthma,^{22 23} atopic



dermatitis²⁴ and eosinophilic esophagitis.²⁵ To date, three biologics have been assessed and approved by the European Union for managing severe CRSwNP,^{26–28} after being studied for asthma: omalizumab, an IgE antibody²⁹; dupilumab, an anti-interleukin (IL)-4- α chain receptor³⁰; and mepolizumab, an IL-5 antagonist.³¹ In France, only dupilumab and mepolizumab are reimbursed in case of severe uncontrolled CRSwNP despite the use of nasal and systemic corticosteroid and endoscopic sinus surgery. Indirect treatment comparison suggests that dupilumab may be superior to mepolizumab in symptom control and QoL outcomes although the patients included in the studies were not similar between the two groups.^{32–33} To date, a few studies reported ‘real-life’ prospective assessment of biologics in CRSwNP.^{34–35} Two observational cohorts showed that a partial control was at least achieved in, respectively, 98.8%³⁴ and 93.8%³⁵ of patients at 12 months of follow-up. The criteria for good to excellent response still need to be defined.²¹ To date, there are no available data regarding the real-life efficacy of mepolizumab in CRSwNP management, except in subgroup analysis of asthmatic patients or in retrospective studies.^{36–37} Waiting for head-to-head biologics comparison, future studies should report the efficacy and safety of biologics in large real-life cohorts. Also, it is important to note that repeated endoscopic sinus surgery is more cost-effective than long-term use of biologics,^{35–38–39} which must be taken into consideration when prescribing biologics.

The EPOS/EUFOREA 2023 update on the indication and evaluation of biologics in CRSwNP recommends considering biologics in uncontrolled patients despite appropriate medical and surgical management, when they fulfil at least three criteria among the presence of ‘type 2 inflammation, regular need for systemic corticosteroids, significant impact on QoL, loss of smell and comorbid asthma’.⁴⁰ The treatment response should be assessed at 6 months, and switching biologics is to be considered in case of poor/absence of response or after a loss of efficacy after an initial good response. Brkic *et al* described the outcomes after switching in 23 patients among 195 treated with biologics.⁴¹ 17 patients switched from omalizumab to dupilumab, with success regarding the nasal polyp score (NPS), asthma control test and Sino-Nasal Outcome Test-22 (SNOT-22) score. There is still a need for real-life data registries to define the appropriate timing and modalities of switching.⁴⁰

This study protocol (V.2.0, 5 April 2022) describes the aims and methods of an ongoing prospective, observational, national, multicentric cohort of patients with CRSwNP treated with biologics.

STUDY OBJECTIVES

This study aims to assess the efficacy and tolerance of biologics in patients with CRSwNP, with or without association with other type 2 diseases, and to determine the strategies in case of uncontrolled disease under biologics. Specifically, we aim to do the following: (a) assess the

6-month and (b) 18-month QoL outcome of patients treated with biologics; (c) study the biological, radiological and clinical outcomes; (d) study the use of systemic corticosteroids and surgical procedures under biologics; (e) study the adverse events of biologics; and (f) study the therapeutic strategy in the follow-up of patients under biologics. We hope that this real-life assessment of dupilumab and mepolizumab, prescribed for recurrent CRSwNP after previous surgery, will provide insight into biologics safety, CRSwNP control, biomarker relevance and switching modalities, to fulfil the unmet needs outlined in EPOS/EUFOREA update.⁴⁰

METHODS AND ANALYSIS

Study design

The BIOlogics in severe nasal POLyposis SurvEy (BIOPOSE) is a French multicentred prospective observational cohort study launched in February 2022 and still ongoing. It is embedded into routine patient care of participating centres, and patients continue to be managed according to local procedures and protocols. The choice of biologics prescribed is not randomised at inclusion. The study is hosted at the University Hospital of Lille, France.

Patients’ data are collected prospectively. Baseline information is collected at the enrolment and follow-up data during follow-up visits at the participating centres. The BIOPOSE has a 300-patient endpoint but will be extended as a permanent national registry. Patient follow-up is planned for a minimum of 3 years and will be extended into the registry.

Study population

Inclusion criteria

Patients over 18 years old requiring biologics for CRSwNP in accordance with its marketing approval in France (ie, severe nasal polyposis, with lack of control under nasal corticosteroid, systemic corticosteroids and surgery) are invited to participate in BIOPOSE.

Exclusion criteria

Patients are excluded in case of:

- ▶ Systemic corticosteroid medication during the 4 past weeks
- ▶ Biological treatment with anti-IgE (omalizumab), anti-IL-5/IL-5R (mepolizumab, benralizumab) or anti-IL-4/IL-13R (dupilumab) or any other biotherapy for inflammatory diseases in the previous 6 months apart from ongoing biotherapies for severe asthma
- ▶ Hypersensitivity to humanised antibodies
- ▶ Documented SARS-Cov2 infection in the last 3 months with persistent olfactory disorders related to COVID
- ▶ Pregnant or breastfeeding women
- ▶ Patient without social coverage

Participating centres

Patient recruitment has started at the following centres:

- ▶ University Hospital of Lille, France
- ▶ University Hospital Bicêtre Paris-Sud, France
- ▶ University Hospital of Bordeaux, France
- ▶ University Hospital of Clermont-Ferrand, France
- ▶ Centre Hospitalier Intercommunal Creteil and University Hospital Henri Mondor, France
- ▶ University Hospital of Lariboisière, Paris, France
- ▶ University Hospital of Nancy, France
- ▶ University Hospital of Nantes, France
- ▶ La Conception University Hospital, Marseille, France
- ▶ University Hospital of Toulouse, France
- ▶ University Hospital of Nice, France
- ▶ University Hospital of Montpellier, France
- ▶ University Hospital of Lyon, France
- ▶ University Hospital of Poitiers, France
- ▶ Institut Arthur Vernes, Paris, France

The laboratory centre for an ancillary biological study is:

- ▶ University Hospital of Lille, France

After the establishment of the study in these initial BIOPOSE clinics, we will invite more centres to join the study and begin patient recruitment.

Patient and public involvement

The trial will be conducted in accordance with the protocol approved by the French Committee for the Protection of Individuals, in compliance with the French Public Health Code, European Union Good Clinical Practice (GCP) and applicable regulatory requirements. The results of the study will be published

in scientific journals and presented at scientific conferences to raise awareness about biologics efficacy and safety in real life.

Study procedures

Figure 1 summarises the study protocol.

Patient identification and recruitment

Eligible patients are identified and invited to participate in the study. They receive all study information from the local recruitment centre. Patients are recruited during a clinical follow-up visit. There might be small variations in recruitment and data collection between participating centres due to the clinical routine of each centre.

Clinical assessments

Eligible patients are followed regularly in each participating centre. The first visit (V0) corresponds to the inclusion and prescription of the biologics. V1 and V2 are planned every 3 months, and then patients will be followed every 6 months until completion of the study. At each visit, patients undergo a complete sinonasal examination using rigid or flexible fiberoptic endoscope. Patients will not be subjected to additional invasive measurements solely for the purposes of the study; examinations and tests are only done if clinically indicated or as part of the local follow-up protocol. All examinations and tests are performed following the local standard operating procedures of the clinic.

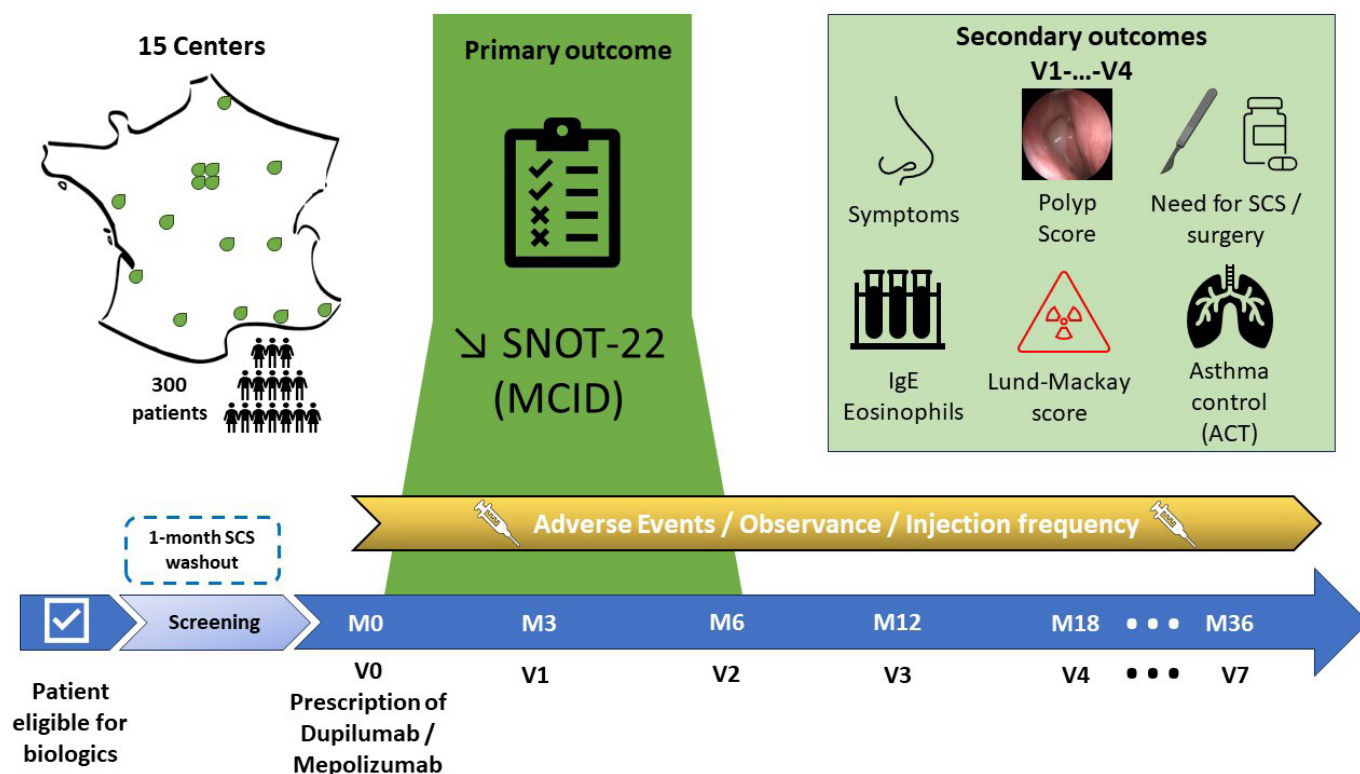


Figure 1 Overview of BIOlogics in severe nasal POLyposis SurvEy study protocol. MCID, minimal clinically important difference; M, month; SCS, systemic corticosteroids; SNOT, Sino-Nasal Outcome Test-22; .

V0: patient recruitment	Follow-up visits & Frequency	
<ul style="list-style-type: none"> • Comorbidities: atopic disease, asthma, aspirine intolerance, sulfite intolerance, chronic otitis media, obstructive sleep apnea, gastroesophageal reflux disease, other significant comorbidity • Topical medication: nasal corticosteroids, nasal rinses • Use of systemic corticosteroids and efficacy on nasal obstruction and olfaction • Use of macrolids • Past endoscopic sinus surgery procedures: number, type and timing • Past biologics used for CRSwNP or asthma • Smoke status • SNOT-22 questionnaire • In comorbid asthma patients: <ul style="list-style-type: none"> • ACT • GINA 2021 medication status • Number of exacerbation / hospitalization / resuscitation for asthma in the past year • Nasal endoscopy: nasal polyp score • Sinus CT scan: Lund-Mackay score • Blood sample: total IgE concentration, blood eosinophilic count • Nasal congestion score • Visual analogic scale of symptoms: <ul style="list-style-type: none"> • Nasal obstruction • Smell lost • Rhinorrhea • Craniofacial pain • Global sinonasal symptoms • Information on management of CRSwNP with biologics • Strategy of biologics prescription 	<ul style="list-style-type: none"> • Biologics used: molecule, adverse events, reason for stopping (if required) • SNOT-22 questionnaire • In comorbid asthma patients: <ul style="list-style-type: none"> • ACT • GINA 2021 medication status • Number of exacerbation / hospitalization / resuscitation for asthma in the past year • Nasal endoscopy: nasal polyp score • Topical medication: nasal corticosteroids, nasal rinses • Use of systemic corticosteroids • Type and timing of surgical procedures after introduction of biologics • Sinus CT scan: Lund-Mackay score • Blood sample: total IgE concentration, blood eosinophilic count • Visual analogic scale of symptoms: <ul style="list-style-type: none"> • Nasal obstruction • Smell lost • Rhinorrhea • Craniofacial pain • Therapeutic strategy for biologics prescription, including switching of biologics. 	Each visit Each visit Each visit Each visit Each visit Each visit Each visit Each visit Each visit Each visit At M6 M3, M6, M12, M18 Each visit Each visit

Figure 2 Overview of the information collected during the BIologics in severe nasal POlyposis SurVEy study.

Data collection instruments

For the collection of patient data, we use standardise CRSwNP-specific instruments, allowing a standardised and validated measurement of outcomes. Only a clinical research assistant will be involved in data collection and monitoring. [Figure 2](#) provides a summary of the information collected from participating patients at the baseline (V0) and follow-up visit.

SNOT-22

SNOT-22 is a patient self-administered dedicated chronic sinusitis QoL questionnaire used to follow the outcomes of medical and surgical endoscopic endonasal procedures.^{1 40 42} SNOT-22 comprises 22 items grouped into 5 domains: rhinologic symptoms, extranasal rhinologic symptoms, ear/facial symptoms, psychological dysfunction and sleep disfunction.⁴³ Each item is scored from 0 (no problem) to 5 (problem as bad as it can be) with 2-week recall, resulting in a total score ranging from 0 to 110 points. The minimal clinically important difference (MCID) value is set at 8.9 points.⁴⁴ It has been translated and validated into French language.⁴⁵ This questionnaire is fulfilled by the patient at each visit.

Asthma control test

Asthma control test (ACT) is a patient self-administrated questionnaire dedicated to asthma control.⁴⁶ It comprises five items scored from 1 (not controlled) to 5 (completely controlled), with a 4-week recall. The scores range from 5 (poor control of asthma) to 25 (complete control of

asthma), with higher scores reflecting greater asthma control. An ACT score >19 indicates well-controlled asthma. ACT is fulfilled by all patients with comorbid asthma at each visit.

Nasal polyp score

Nasal endoscopy is performed to determine the NPS,²⁷ rated for each side as follow: 0, no polyp; 1, polyp remaining in the superior part of the middle meatus; 2, polyps extended to the inferior part of the middle turbinate but without extension below the superior third of the inferior turbinate; 3, polyps extended to the level of the inferior turbinate, without reaching its inferior third; and 4, polyps leading to a complete obstruction of the nasal fossa. The total NPS ranges from 0 to 8 points.

Lund-Mackay score

Lund-Mackay score (LMS) is a staging system radiologic score, based on sinus opacity on CT scan examination,⁴⁷ with a good interobserver reliability.⁴⁸ This score ranges from 0 (complete lucency of all sinuses) to 24 (complete opacity of all sinuses) and is interesting to predict CRSwNP severity in association with SNOT-22.⁴⁹

Symptoms scores

To assess the impact of the main symptoms of CRSwNP, 0–100 visual analogue scales of nasal blockage, rhinorrhea, facial pain and global symptoms will be recorded.^{50–52} The nasal congestion score, used in most of biologics phase III studies,^{26–28} ranges the nasal congestion symptom from 0

to 3. Smell loss will be assessed using a visual analogical scale (VAS), and all centres are not equipped with olfactory testing tools.

What information is collected

Figure 2 provides a brief overview of the information collected from participating patients at the baseline and follow-up visits, including the minimum required data, which are assessed for all patients in all participating centres. The patients already treated with biologics for CRSwNP before February 2022 will be followed, and their previous clinical and biological data will be retrospectively collected.

ENT examinations

The ears, nose and throat (ENT) examinations performed in the participating centres include nasal endoscopy (either rigid or flexible) to record the NPS as described above: nasal congestion score (0–3) and VAS for each nasal symptom (0–10) at each visit—nasal obstruction, smell lost, rhinorrhea, craniofacial pain are recorded. Topical medication used (nasal corticosteroids and/or nasal rinses), the use of systemic corticosteroids (number of courses) and other past treatments (macrolides or else) are also recorded. Type and timing of past surgical procedures and/or time to surgery after introduction of biologics are collected. The biologics used, molecule, dose, duration, adverse events and reason for stopping (if required), are recorded as well as the therapeutic strategy for biologics prescription, including switching of biologics. A general physician and a dermatologist can request any extra follow-up visit to help us monitor the side effects. The choice of biologics prescribed is not randomised at inclusion. While respecting the scope of the molecule's authorisation and the criteria for reimbursement in France, the decision to treat, the choice of biologics, the methods of administration and the duration of treatment are left to the discretion of the physician managing the patient. Patients whose biologics prescribed at inclusion is discontinued or modified during the standardised 18-month follow-up period continue to be monitored according to the monitoring schedule (M0, M3, M6, M12 and M18). During this follow-up period, the need for surgery and/or systemic steroids will follow the French ENT Society guidelines regarding CRSwNP.²¹ Therefore, patients will undergo surgery or a course of systemic steroids while under biologics in case of uncontrolled severe disease based on nasal symptoms and the impact on their QoL. Blood samples are performed at initial visit, M3, M6, M12 and M18 to look for T2 inflammation biomarkers (blood eosinophilic count and total IgE concentration). Indeed, several studies have shown that CRSwNP is associated with a T2 immune response leading to B cell release of IgE, mucosal recruitment of eosinophils from bone marrow via IL-5-mediated, IL-4-mediated and IL-13-mediated chemoattractant production.^{24 53 54} Sinus imaging is performed at 6 months, and the LMS is assessed.

Other data from clinical records

At recruitment, baseline medical information and comorbidities (atopic disease, asthma, aspirin intolerance, sulfite intolerance, chronic otitis media, obstructive sleep apnea, gastro-oesophageal reflux disease and other significant comorbidities) are collected from clinical records. In comorbid asthma patients, ACT, Global Initiative for Asthma 2021 medication status and the number of exacerbation/hospitalisation/resuscitation for asthma in the past year will be collected.

Information on questionnaires

Participating patients are asked to complete the SNOT-22 questionnaire at every visit and the ACT in case of comorbid asthma as described above.

Ancillary study

An ancillary study is conducted on patients recruited in one centre, the University Hospital of Lille, France, for CRSwNP endotyping. A specific consent is obtained from participants.

Biomarkers are studied at M0 (V1), M3 (V2), M6 (V3), M12 (V4) and M18 (V5), which are not part of a clinical routine:

- ▶ Serum concentration of eotaxin-1, eotaxin-2, eotaxin-3, IL-4, IL-5, IL-13, thymus and activation-regulated chemokine (TARC), thymic stromal lymphopoietin (TSLP)
- ▶ Expression of CD125, CD123, CCR3, Human Leucocyte Antigen - DR isotype (HLA-DR), CD69 and CD44 on circulating eosinophils
- ▶ T-cell polarisation: expression of CD3, CD4, CXCR3/CD183, CCR6/CD196, CCR4/CD194 and "Chemoattractant receptor-homologous molecule expressed on Th2 cells" (CRTH2 in flow cytometry)

Study database

All collected data are entered into a secure web-based database using a widely used software, Research Electronic Data Capture, hosted by the University Hospital of Lille, France. Contributing centres are responsible for the pseudonymisation of the data contributed to the study. The software enables the development of an electronic case report form. Before freezing the database, data will be monitored according to the consistency rules agreed with the project manager. Access to data will be restricted to those directly involved in the study: local investigators have access only to data from their centre. Data may only be modified by an investigating physician participating in the study or by a collaborator designated by this physician and participating in the study. Data generation, transmission, storage and analysis of health-related personal data within the study follow the French legal requirements for data protection ("Règlement Général sur la Protection des Données" RGPD). Data regarding this study will be stored for a minimum period of 15 years from the end of the research or its early termination, without prejudice to the ongoing administrative procedures.



Study power and sample size

We expect to recruit at least 300 patients in BIOPOSE, but our task is to expand recruitment beyond 300 patients and establish a permanent and nationwide cohort. Indeed, after the establishment of the cohort, it will be possible for more centres to join and contribute to patients, resulting in a higher cohort. The main aim of the study is to estimate the evolution of patients' QoL using the SNOT-22 score at 24 weeks of treatment. The primary endpoint is the frequency of patients improving their QoL, improvement being defined as a change in QoL between baseline and 24 weeks greater than the MCID in absolute value (8.9).⁴⁴ The number needed to treat is based on literature and the proportion of patients improved estimated. In the two Phase III trials evaluating omalizumab in CRSwNP (POLYP 1 and POLYP 2),²⁷ 69 and 58 patients, respectively, in the omalizumab arm had completed the study protocol. The change in SNOT-22 score at 24 weeks of treatment was $-24.70 (\pm 2.01)$ and $-21.59 (\pm 2.25)$, respectively (\pm SEM), that is, SD of 16.7 and 17.3, respectively, exceeding the accepted threshold of MCID (8.9, 30). In the two Phase III trials evaluating dupilumab in CRSwNP (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52),²⁶ 124 and 282 patients, respectively, in the dupilumab arm had completed the study protocol. The change in SNOT-22 score at 24 weeks of treatment was $-30.43 (\pm 1.54)$ and $-27.77 (\pm 1.26)$, respectively (\pm SEM), that is, SD of 14.0 and 21.1, respectively, again exceeding the MCID.³⁸ Based on these data, and assuming a Gaussian distribution for variation in QoL, we estimate improvement frequencies of 83%, 77%, 94% and 81% for these four trials. We assumed an expected frequency of 80%. We set the relative precision at 10% or 8% in absolute terms (precision is defined by the half-width of the 95% CI). Under these assumptions, 100 patients will be required. Given the latest arrival of mepolizumab, 1 year after dupilumab in France, we seek to recruit 300 patients to have a representation of the two biologics in the database. The parameters of randomisation and blinding do not apply to our cohort study describing patients treated with the same therapeutic modality. Selection bias is reduced by compliance with the authorisation for biologics. Measurement bias is limited by the prospective nature of the analysis. Information bias is prevented by the choice of a French-validated QoL questionnaire (SNOT-22) as the primary endpoint, for which the MCID has been established in the literature.

Planned analysis and outcomes of interest

All statistical analyses will be carried out independently within a dedicated unit of methodology, biostatistics and data management (UMBD) of Lille University Hospital, under the supervision of Professor Alain Duhamel. The software used will be SAS V.9.4 or more recent. All data collected will be described. Qualitative variables will be described in terms of numbers and percentages. Quantitative variables will be described by the mean and SD in the case of a Gaussian distribution or by the median and

IQR (ie, 25th and 75th percentiles) in the opposite case. The normality of distributions will be tested by a Shapiro-Wilk test and verified graphically by histograms. The main outcome is the proportion of patients with SNOT-22 MCID achievement (reduction of 8.9 points or more) at 6 months of follow-up (figure 1). BIOPOSE will also study the therapeutic strategy when modifying the prescription (reasons to dose down, stop or switch biologics) during the first 18 months. Positioning of biologics in the treatment pathway of patients, describing combination therapy (surgery and biologics), identification of clinically relevant biomarkers to select responders and reporting adverse effects with long-term use are clearly in the scope of BIOPOSE.

Regarding secondary objectives are as follows: (1) To describe the evolution of patients' QoL using the specific SNOT-22 score since the initiation of biologics and during the 18 months of standardised follow-up. The evolution of the SNOT-22 scores at M0, M3, M6, M12 and M18 will be studied using the linear mixed model to take into account correlations between repeated measurements on the same patient. The covariance matrix (compound symmetry, AR¹ or unstructured) will be chosen according to the Akaike Information Criterion. The validity of the model will be studied by residual analysis. The same method will be used for secondary objectives 2 and 5 (changes in VAS and blood levels of eosinophils and total IgE). (3) Evaluate systemic corticosteroid sparing since the initiation of biologics and during the 18 months of standardised follow-up. The number of courses of systemic corticosteroids (per intraosseous infusion or intravenous) received by the patient and that received before each visit will be compared using a generalised linear mixed model (Fish distribution, log link, patient random effect and offset corresponding to observation time). Relative risk (after vs before) will be calculated as effect size with 95% CI. If the hypotheses of the Fish model are not verified, we will use a model with a negative binomial distribution or, failing that, a paired Wilcoxon test. (4) The time to the first endoscopic surgical procedure during the 18 months following biologics initiation will be estimated by the Kaplan-Meier method. The 95% CI will be calculated. (6) The evolution of polyp size at nasal endoscopy (ordinal variable coded from 0 to 4) according to measurements at M0, M3, M6, M12 and M18 will be studied by a generalised estimating equations (GEE) model, GENMOD procedure on SAS software, to account for correlation between repeated measurements. (7) The cumulative total dose of systemic corticosteroids in the year following the initiation of biologics and the cumulative total dose of oral corticosteroids in the year preceding the introduction of biologics will be compared by a paired Student's t-test in the case of a normal distribution or a paired Wilcoxon test in the opposite case. (8) Nature and date of the last sinonasal procedure for CRSwNP. (9) Evolution of Lund-Makay score between M0 and M6. (10) Adverse events and severe adverse event report. (11) ACT score evolution in the first 18 months.

(12) Comparison between asthma exacerbation in the 12 months before introduction of biologics and the 18 months after, using the method described for objective 3 (Poisson model). (13) Proportion of patients discontinuing biologics treatment in the 18 first months. (14) Parameters 1–6 according to the asthma status. (15) Symptoms of patients under biologics from 18 to 36 months. (16) Sinonasal symptoms in patients discontinuing biologics between 18 and 36 months. (17) Therapeutic strategies during follow-up (reasons for dosing down, stopping or switching biologics). For secondary objectives 8–11, 13, 14, 16 and 17, we will use descriptive analyses.

An ancillary study is conducted on patients from Lille, France, and in centres that can technically meet sample storage and transport constraints, focusing on objectives 18–21. (18) Evolution of eotaxin-1, eotaxin-2, eotaxin-3, IL-4, IL-5, IL-13, TARC and TSLP in the first 18 months of follow-up. (19) Expression of CD125, CD123, CCR3, HLA-DR, CD69 and CD44 on circulating eosinophils and their evolution during the first 18 months of follow-up. (20) Lymphocytes' immune response polarisation in the first 18 months of follow-up. For objectives 18–20, we will use descriptive analyses and, if possible (depending on model validity), the linear mixed model described for secondary objective 1. For secondary objective 21, if possible, depending on model validity, we will also use a linear mixed model with a fixed effect for the presence of asthma. Otherwise, we will use descriptive analyses. All missing values will be described in detail; however, we expect this will not be an issue for the important variables as the data are collected prospectively. In case we have a significant amount of missing data, we will consider subgroup analyses or multiple imputation of missing data to deal with this issue, depending on what is the most appropriate approach for the specific question and analysis.

Committees

The scientific steering committee is composed of Dr Guillaume Lefèvre and Professor Jean-François Papon. Its role is to provide scientific approval of the protocol.

No independent data monitoring committee is required for this phase IV observational study. A senior clinical research associate will be responsible for auditing and on-site monitoring visits to check for patient information and consent, inclusion criteria, main study outcomes and adverse event monitoring and declaration. A clinical research associate will be responsible of data management on each centre. The declaration of adverse event will be the responsibility of each investigator.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance with the approved protocol, in compliance with the French Public Health Code, European Union GCP and applicable regulatory requirements. The trial was approved by the French

Committee for the Protection of Individuals and registered on the public database ClinicalTrials.gov. Protocol amendments will be communicated to all relevant parties.

In accordance with current regulations, patients included must receive fair and complete information, written on the Information Letter, specially drafted and validated by the French Committee for the Protection of Individuals, which must be provided and explained by the investigator. In particular, the investigator must inform the participant of the possible risks and constraints of participating in the trial. The participant will be able to ask any questions he or she may have and will be given the time he or she needs to make an informed decision.

The participant must then sign the consent form (see online supplemental appendix 1) with the investigator who presented the trial, and this document must be dated the day of signature. One copy will be given to the participant, one will be kept by the investigator in the participant's medical file and one will be given to the sponsor in a sealed envelope.

In accordance with the methodology of reference (MR 001), data processing will be carried out under the conditions of confidentiality defined by the amended law of 6 January 1978, relating to information technology, files and freedoms as well as in compliance with the European Regulation (General Data Protection Regulation: GDPR). The data controller is the promoter, Lille University Hospital. In accordance with the GDPR, the data from this study will be processed for scientific research purposes (Article 6) as part of the performance of a public interest mission (Article 9) in which the promoter is involved. Data from this study will be stored in the University Hospital computer network. The data collected will be pseudonymised.

The results of the study will be published in scientific journals and presented at scientific conferences to raise awareness about biologics efficacy and safety in real life (see Standard Protocol Items: Recommendations for Interventional Trials guidelines, online supplemental appendix 2). The principal investigator of the study affirms and upholds the principle of the participants' right to dignity, privacy and health and that the project team shall comply with applicable privacy laws. Specifically, the anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual participant medical information obtained during this research project is considered confidential and will not be disclosed to third parties.

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