Title Page

Protocol Title: Nation-wide health resource consumption and costs associated with mepolizumab (Nucala): a French SNDS database study

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Short Title: Nation-wide health resource consumption and costs associated with mepolizumab (Nucala)

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1. Introduction

1.1. Study Rationale

Currently, no study has addressed real-life data describing changes in health resource consumption and related costs attributable to mepolizumab treatment. The aim of the current study is to fill this knowledge gap by performing an exhaustive extraction of data for patients receiving mepolizumab in the French single-payer health care system (via the national health data system or 'SNDS'). The change in real-life health-resource usage and costs observed for these patients would provide the first evidence that mepolizumab is changing the care landscape for eligible severe asthma patients.

1.2. Benefit/Risk Assessment

This study will be performed exclusively using French national claims database data (SNDS). As a non-interventional study based on secondary use of of medico-administrative data, it meets requirements for a 'European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (EnCEPP) study'. Safety-relevant results will be presented as aggregated data only.

The reader should note that the current knowledge on mepolizumab indicates a list of quite minor side effects (injection site reactions, lower respiratory tract infections, urinary infections, pharyngitis, headache, back pain, and others as mentioned in the Summary of Product Characteristics). Compared with the long-term use of oral corticosteroids (OCS) or short acting beta antagonists (SABA) (currently the most-used anti-asthma medications)(Nwaru et al. 2020), whose side effects include adrenal insufficiency, diabetes, and increased mortality (Zazzali et al. 2015; Sweeney et al. 2016; Barry et al. 2017; Zeiger et al. 2017; Daugherty et al. 2018; Sullivan et al. 2018; Nwaru et al. 2020), mepolizumab initiation is hypothesized to not only decrease the costs associated with recurrent severe asthma, but also costs purportedly due to the comorbid burden associated with rescue medicine.

1.3. Limitations of the study design

Potential limitations of the study are related to the use of claims data, especially the completeness of prospectively accrued data and the paucity of clinical or biological data.

The SNDS provides clinical information about a specific disease only through coded discharge diagnoses and recorded Long Term Illnesses (ICD-10 codes), and the drug and medical devices used. The identification of patients with a certain disease or comorbidity often depends on the development of algorithms taking into account different combinations of hospital diagnoses or types of delivered drugs.

The SNDS does not provide paraclinical information and other risk factors such as smoking, weight, or body mass index (except when coded within hospitalization data). For the present study, no subgroup can be defined to assess mepolizumab exposure according to weight/bmi. However, age and sex subgroups can be defined. Drug related adverse events are not reported in the SNDS, so traditional safety analyses are not possible.

Mepolizumab exposure is based solely on its delivery; the actual exposure of the patient to the delivered drug is not measurable in this secondary database study, and this limitation should be mentioned in subsequent publications.

The overwhelming strength of the SNDS database is that it is one of the largest continuous countrywide claims databases. It covers just about the whole population (99%) essentially from birth to death, irrespective of the health care provider, age or socioeconomic status, and retirement status (Bezin et al. 2017). Patients keep the same identifier throughout their lifetime, and there are no restrictions in coverage related to income or social situation. At this point about 600 million patient years of data are stored, though not all are immediately accessible.

There are no risks to patients associated with study execution or study findings.

2. Objectives and Endpoints

In light of the clearly documented clinical efficacy of mepolizumab for the treatment of asthma, our hypothesis is that mepolizumab treatment results in decreased consumption of health care resources, with corresponding decreases in overall costs for the single payer social security health insurance program in France.

The overall objectives of this study are: (i) using the SNDS French national database, to identify a representative, nation-wide population of patients treated with mepolizumab with a follow-up period of at least 12 months, (ii) to describe the initial one-year changes in health resource use before and after the initiation of mepolizumab treatment and (iii) to estimate the change in associated costs for the first year of treatment. These initial data will additionally serve as a basis for the design of longer-term studies.

Information available in the SNDS

The available **beneficiary characteristics** include date of birth, gender, area and region of residency, universal medical coverage status, and complementary health insurance status. Chronic diseases are classified according to ICD codes, with registration and end dates, if applicable. For deceased beneficiaries, the date of death is recorded, with the principal, related and associated causes of death.

Inpatient care is characterized via linkage with the PMSI database and comports the type of hospital (short-stay care, long-stay care and rehabilitation, psychiatry, or home-hospitalization), within-hospital trajectories (for example, passages through emergency departments or intensive care), principal and secondary diagnoses associated with hospital entry, the procedures performed during each stay, the consumption of a special drug category termed “costly drugs”, entry and leave dates and associated mode (transfer, return home), and cost information.

Outpatient care comprises care not affected to a hospital stay and the related data include drug delivery (international non-proprietary name and anatomical therapeutic chemical classification, packaging identifier code, the common dispensing unit, quantity and date of delivery), medical devices (type, quantity and date of delivery), medical visits (date and speciality of the physician),

paramedical visits (date and type (nursing, physical therapy, etc)), medical procedures (date and type), lab tests (date and type), government benefits (beginning and end dates and type (disability, maternity, sick leave, etc), medical transportation usage. Each outpatient care element is further characterized according to professional source and legal status (pharmacy, specialist, nurse, therapist, etc), the area and region of residency, the price presented for reimbursement and the amount actually reimbursed by the single payer system.

Describing the population

The index date "T0" is defined as the day upon which the beneficiary received a first dose of mepolizumab. Population characteristics will be tabulated at this time point and will include age, gender, area and region of residency, universal medical coverage status, and complementary health insurance status.

The population will be further described by providing the duration of treatment with mepolizumab (ie medication persistence (Cramer et al. 2008), defined as date of last administration – T0 in days) as well as the proportion of days of follow-up covered (PDC) by mepolizumab. The current authorized dosage for mepolizumab is a single 100 mg subcutaneous injection every 4 weeks (with an authorized leeway of +- 7 days), and the PDC will be determined accordingly.

Drug consumption

All drug consumption will be analyzed, with specific attention given to (i) mepolizumab, (ii) corticosteroids (oral/IV/systemic, inhaled, topical, etc), asthma-specific medications (selective beta-2-adrenoreceptor agonists, adrenergics in combination with corticosteroids or other drugs, anticholinergics, adrenergics for systemic use, xanthines, leukotriene receptor antagonists, other systemic drugs for obstructive airway diseases, etc), and diabetes-related medications (buiguanides, insulin, etc). Drugs demonstrating significant changes in cumulative dose between the baseline and exposure periods (if any in addition to mepolizumab) will be identified.

Hospitalizations

The following will be compared between baseline and exposure periods: (i) the number of hospitalizations for asthma (the corresponding primary diagnosis ICD10 codes are Predominantly allergic asthma (J45.0), Nonallergic asthma (J45.1), Mixed asthma (J45.8), Asthma, unspecified (J45.9), and Status asthmaticus (J46)), (ii) the number of hospitalizations in general (all causes), (iii) the cumulative days of hospitalization (in association with asthma and for all causes), (iv) the cumulative days of intensive care (in association with asthma and for all causes). Each day of hospitalization can be considered as a recurrent event.

Consultations

The cumulative numbers of consultations will be compared between the baseline and exposure period and differentiated according to type (general and specialist medical consults, nursing and other paramedical consults etc). Special attention will be given to pulmonology/allergology and metabolic/endocrine specialist consults, as well as nursing consults for injections.

Assessments/procedures

Information concerning the laboratory and imaging assessments performed is available, but not their results. Special attention will be given to lung function, adrenal function, glycemia, and bone

density assessments. The cumulative numbers of different assessments will be described and contrasted between the baseline and exposure periods.

Diagnoses / Comorbidities

Resource-use algorithms will be developed as indicators of severe asthma (via a combination of specific asthma controllers and oral corticosteroids), uncontrolled asthma (combinations of oral corticosteroids, hospitalization for asthma, specialist and/or emergency care usage), chronic obstructive pulmonary disease and diabetes (specific drug deliveries). Evidence of further comorbidities will be collected (via a specific list of long-term diseases, and via the primary and secondary coding performed during hospitalizations) and their incidence before versus after T0 studied.

Costs

Cumulative per-beneficiary costs (including all health care resource uses and government benefits) will be described and contrasted between the baseline and exposure periods. This will be performed at several levels: (i) all costs regardless of source or potential link with diagnoses, (ii) costs due to mepolizumab, (iii) costs that can be associated with asthma-specific care, (iv) costs that can be associated with the monitoring and care for certain key comorbidities (diabetes, bone density/osteoporosis).

Subpopulations of interest

Sub populations of interest and subject to comparative analyses include sex, age groups, beneficiaries with versus without indicators of severe asthma, uncontrolled asthma, chronic obstructive pulmonary disease, and diabetes (identified via the prescription of specific drugs, hospitalization diagnoses, assessments or combinations thereof).

Objectives	Endpoints
Primary	
• To estimate the change in associated costs for the first year of treatment	• Total health care costs for the year preceding the initiation of mepolizumab, as well as for the year after.
Secondary	
• To describe the initial one-year changes in health resource use before and after the initiation of mepolizumab treatment	• Cumulative estimates for health resource use and associated costs for the year preceding the initiation of mepolizumab, as well as for the year after.

Tertiary/Exploratory	
• To further characterize rates of change in health resource usage and/or costs in subpopulations of interest	• Sub populations of interest and subject to comparative analyses include sex, age groups, beneficiaries with versus without indicators of severe asthma, uncontrolled asthma, chronic obstructive pulmonary disease, and diabetes (identified via the prescription of specific drugs or combinations thereof).

3. Study Design

3.1. Overall Design

This retrospective, non-interventional (not involving human subjects) database study will compare real-life patient health resource consumption before versus after a first injection of mepolizumab. Data concerning patients receiving mepolizumab will be collated for a 12-month period (the "baseline period") preceding a first index treatment (at "T0") and compared to a 12-month period occurring after the index treatment (the "exposure period")(Figure 5-1).

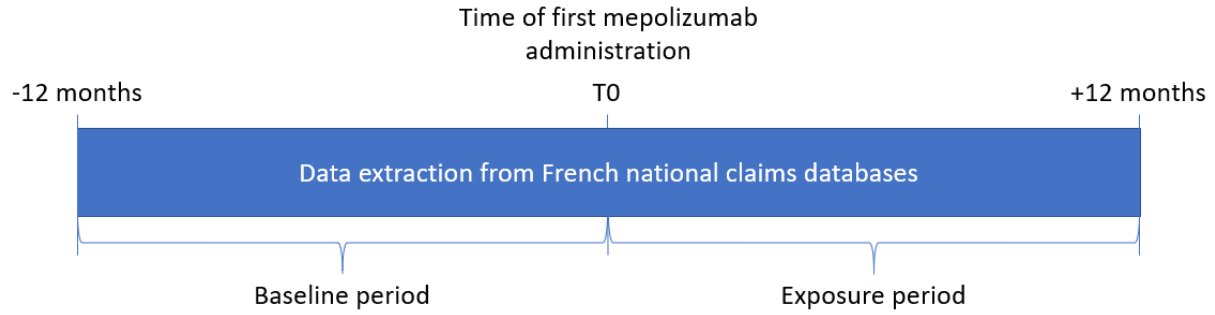

Figure 3-1 Graphic presentation of the basic study design comparing health care resource use data between a one-year baseline period and a one-year exposure period after the first administration of mepolizumab (T0).

The expected correspondence to calendar time (Figure 5-2) is an inclusion period for T0 starting in February 2018 to December 2018, with 12 months of "follow-up" corresponding to the year 2019. It follows that baseline data will reach back to February 2017. If data for exposure periods longer than 12 months are available, these will also be collected to describe future trajectories of health resource use in as much as possible.

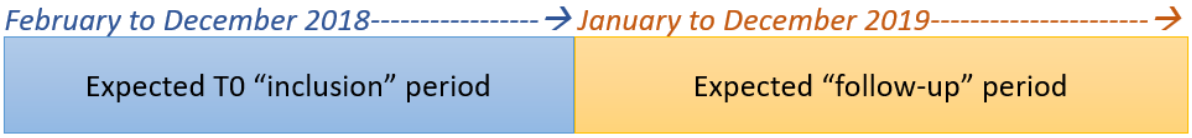

Figure 3-2 The expected correspondence with real time is an inclusion period covering patients who started mepolizumab in the year 2018, with 12 months of "follow-up" in the year 2019.

3.2. Participant and Study Completion

This study is primarily descriptive and the identification of beneficiaries receiving mepolizumab wi ll be exhaustive. In this context, traditional sample size calculations are inappropriate/unnecessary. A first estimate indicates an expected sample size of 2813 patients (see section 10.1)

As concerns exclusion from the analysis due to missing data, we expect this to be minimal as the databases are exhaustive and obligatory concerning drug dispensations.

3.3. End of Study Definition

Patients will be identified as beneficiaries within the French National Health Data System [*Système National des Données de Santé*](SNDS), which covers approximately 66.6 million people, or 99% of the French population (Bezin et al. 2017). **Longitudinal coverage of a given beneficiary stops at death or at when he/she moves abroad (De Roquefeuil et al. 2009).**

Study calendar

PROPOSAL SUBMISSION:	25 November 2019
PROPOSAL OF INTEREST COMMUNICATED BY GSK:	20 January 2020
FIRST DRAFT OF PROTOCOL REQUESTED BY GSK:	29 February 2020
AUTHORIZATIONS/APPROVALS:	April-June 2020
PUBLIC DISCLOSURE/REGISTRATIONS:	May-June 2020 (This is flexible, but must be performed right before data extraction)
DATA EXTRACTION AND WRANGLING:	July-September 2020
ARTICLE WRITING:	February 2020 to November 2020
FIRST SUBMISSION OF ARTICLE:	December 2020

RESULTS REPORTING ON CLINICALTRIALS.GOV:	July-September 2021 (Can be performed earlier, as soon as the princeps article is accepted).

3.4. Scientific Rationale for Study Design

Our goal is to use real-life, exhaustive data to describe 1-year changes in health resource use before and after the initiation of mepolizumab treatment among beneficiaries of the French health insurance program. This goal necessitates the use of the SNDS databases (SNIRRAM, PMSI, BMCD).

3.5. Justification for Dose

Not applicable.

4. Study Population

The study population will comport all beneficiaries in the national French SNDS database who were prescribed mepolizumab and for whom health resource use data is available for the 12 months preceding and following a first filled prescription for mepolizumab.

4.1. Inclusion Criteria

- Beneficiary in the anonymous French national SNDS database
- The beneficiary received mepolizumab

4.2. Exclusion Criteria

- Health resource use data covering the 12 months preceding the first filled prescription for mepolizumab are not available
- Health resource use data covering the time period starting at the first filled prescription for mepolizumab and ending at subsequent death or at 12 months later are not available

4.3. Lifestyle Restrictions

No restrictions are required.

4.4. Screen Failures

Not applicable.

5. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

5.1. Treatments Administered

Not applicable. This is an observational database study during which no drugs are administered. The data do however concern beneficiaries of the French medical system who received mepolizumab in the past.

5.2. Dose Modification

Not applicable to the present database study.

5.3. Method of Treatment Assignment

Only data for beneficiaries who received mepolizumab will be analyzed. Therefore, 100% of the statistical observations / beneficiaries in this study will have received mepolizumab in the past.

5.4. Blinding

Not applicable to the present database study.

5.5. Preparation/Handling/Storage/Accountability

Not applicable to the present database study.

5.6. Treatment Compliance

Medication persistence is defined as the duration from T0 (first injection of mepolizumab) to the discontinuation of therapy (Cramer et al. 2008).

The proportion of days of follow-up covered (PDC) by mepolizumab will also be calculated as the best available proxy for adherence and an important covariate for analyses.

5.7. Concomitant Therapy

All drug consumption available in the SNDS will be analyzed, with specific attention given to (i) mepolizumab, (ii) corticosteroids (oral/IV/systemic, inhaled, topical, etc), asthma-specific medications (selective beta-2-adrenoreceptor agonists, adrenergics in combination with corticosteroids or other drugs, anticholinergics, adrenergics for systemic use, xanthines, leukotriene receptor antagonists, other systemic drugs for obstructive airway diseases, etc), and diabetes-related medications (buiguanides, insulin, etc). Drugs demonstrating significant changes in cumulative dose between the baseline and exposure periods (if any in addition to mepolizumab) will be identified.

5.8. Treatment after the End of the Study

Not applicable to the present database study, which is completely observational and will not affect past, current or future practice/treatment in any way.

6. Discontinuation/Withdrawal Criteria

Not applicable to the present database study, which is completely observational and will not affect past, current or future practice/treatment in any way.

6.1. Discontinuation of Study Treatment

Not applicable to the present database study, which is completely observational and will not affect past, current or future practice/treatment in any way.

6.2. Withdrawal from the Study

Not applicable to the present database study.

6.3. Lost to Follow Up

Not applicable to the present database study.

7. Study Assessments and Procedures

7.1. Efficacy Assessments

Not applicable. No efficacy assessments will take place during this retrospective, observational study. The notion of efficacy is nevertheless represented by an expected decrease in the use of asthma rescue medications during the mepolizumab exposure period.

7.2. Adverse Events

This study will be performed exclusively using French national claims database data (SNDS). As a non-interventional study based on secondary use of of medico-administrative data, it meets requirements for a 'European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (EnCEPP) study'. Safety-relevant results will be presented as aggregated data only.

7.3. Treatment of Overdose

Not applicable to the present database study, which is completely observational and will not affect past, current or future practice/treatment in any way.

7.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

7.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

7.6. Genetics

Genetic evaluations will not be performed in this study.

7.7. Biomarkers

In this non-interventional database study, biomarkers will not be evaluated.

7.8. Medical Resource Utilization and Health Economics

No real-time assessments will be made in this retrospective, observational studies. As described in section 4, all data to be analyzed will originate from French national claims databases.

Patients will be identified as beneficiaries within the French National Health Data System [Système National des Données de Santé](SNDS), which covers approximately 66.6 million people, or 99% of the French population (Bezin et al. 2017). The SNDS provides access to pseudonymised health data from 3 databases ('Composantes Du SNDS | SNDS' n.d.; Bezin et al. 2017). (i) The SNIIRAM (Système National d'Information Inter Régimes de l'Assurance Maladie): the main health care claims database. It provides all reimbursed outpatient and inpatient care for the 3 main French claims systems (CNAM, RSI and MSA) and almost all the smaller systems. (ii) The PMSI (Programme de Médicalisation des Systèmes d'Information) (Boudemaghe and Belhadj 2017) contains information on all reimbursed inpatient care for all beneficiaries, and for hospitals and public or private all care facilities. (iii) The BMCD (Base de données sur les causes médicales de décès) from the national death registry (CepiDC, Inserm) provides causes of death.

The vast majority of variables used in this study correspond to health resource usage and associated costs.

8. Statistical Considerations

8.1. Sample Size Determination

This study is primarily descriptive and the identification of beneficiaries receiving mepolizumab i n the SNDS will be exhaustive. In this context, traditional sample size calculations are not appropriate/unnecessary.

A first, preliminary analysis of the EGB, a 1/97th random permanent sample of the SNIIRAM French national database (Bezin et al. 2017), currently yields 29 beneficiaries having received mepolizumab during the 11 month period starting in February 2018 and ending in December 2018. We therefore aim to analyze data for approximately 29 x 97 = 2813 beneficiaries receiving mepolizumab with 1 year of follow-up time.

Considering a type I error rate of 5% (α=0.05), a sample size of 2813 yields *a posteriori* power estimates of 90% or better for cohen's effect sizes superior to 0.063 (Figure 10-1). The latter indicates ample power to detect very small effects (an effect size of 0.2 is considered as "small").

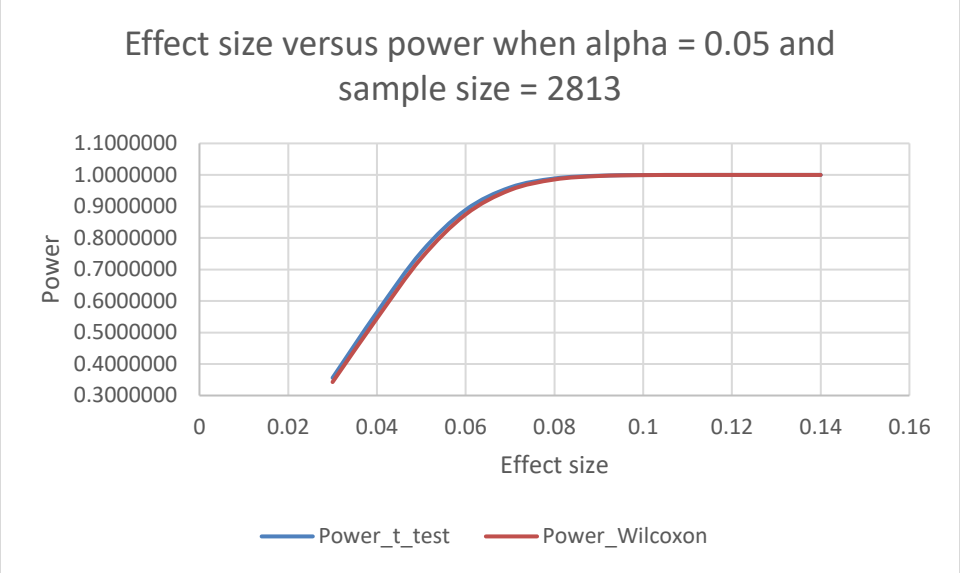

Figure 8-1 Effect size versus power for paired t-tests or for paired Wilcoxon tests (non-parametric option) when the type 1 error rate is set at alpha=0.05 and a sample size of 3000 is expected.

NB: This preliminary sample size analysis also served as a testing ground for the primary patient-selection algorithm (based on medication codes UCD 9413850 // code CIP_C13 3400930038352), which is now finalized.

8.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Evaluable	All lines of data that are included and not excluded will enter the analysis.

8.3. Statistical Analyses

8.3.1. General considerations

Children and adult patient data will be analyzed (no age limits will be imposed).

Descriptive statistics for quantitative variables will include sample size and number of missing values, range, median (interquartile range), and mean ± standard deviation. Summary statistics for qualitative variables will include sample size and number of missing values, the frequency and percentage (over non-missing values unless otherwise specified) for each category. All applicable statistical tests will be performed using a bilateral 5% significance level. All confidence intervals (CI) presented will be 95% and two-sided.

The lost to follow-up patients (e.g. exit from one of the insurance schemes available in the SNDS, expatriation with exit from French insurance schemes) will not be included in the study. No replacement of missing values will be performed. For a given patient with a complete follow-up period, all reimbursed healthcare consumptions are reported in the database.

8.3.1.1. Mepolizumab exposure

Mepolizumab exposure will be characterized by cumulative numbers of injections and dosage.

Medication persistence is defined as the duration from T0 to the discontinuation of therapy (Cramer et al. 2008)(or the end of follow-up for the present study).

The proportion of days of follow-up covered (PDC) by mepolizumab (or the anologous medication possession ratio for dispensations) will also be calculated as the best available proxy for adherence and an important covariate for analyses or defining subgroups.

If mepolizumab is administered during a hospital stay, the dispensation might not be captured. This possibility will be explored by juxtaposing uncovered (non-PDC) time with hospital stays and investigating two extreme hypotheses: either all such stays contained the missing administration, versus no such stays contained the missing administration. This will provide minimum and maximum possible ranges for mepolizumab exposure.

8.3.1.2. Costs

Economic assessments will be performed based on the Health Insurance (costs endorsed by national health insurance) and Collective (complementary insurance and remaining out of pocket charges) perspectives. For the Health Insurance perspective, the consumption of care will be valued according to the amounts reimbursed, and, for the Collective perspective, according to the amounts presented for reimbursement. In the latter, the hospitalizations will be valued according to the costs resulting from the ENCC (National Study of Costs with Common Methodology). All costs will be discounted to the year corresponding to the data access date.

8.3.1.3. Statistics associated with specific endpoints

Endpoint	Statistical Analysis Methods
Primary (total costs)	Differences between the two study periods will be presented with their 95% confidence intervals, as well as significance testing for paired data (see the next section (10.3.2)). Changes in total costs with time will also be visually presented using mean cumulative function step curves (see section 10.3.3).
Secondary (health resource use and sub-costs)	The same strategies as for the primary endpoint will be employed (see the next section (10.3.2)).
Sub group analyses	The same strategies as for the primary endpoint will be employed (see the next section (10.3.2)).

8.3.2. Comparing health resource usage and costs before and after T0

Descriptive statistics for the different types of health resource usage and their associated costs will be calculated for both the baseline and exposure periods. Differences between the two study periods will be presented with their 95% confidence intervals. Statistical techniques for paired data (paired t-tests, paired Wilcoxon tests) will be used to compare variables between the two periods. Potential covariates/subgroups-of-interest will be tested via interaction terms (covariate x period interactions) in mixed models with patients as fixed effects or via regression models explaining the change in resource use (Δbaseline period-exposure period). Due to the descriptive and exploratory nature of this study, results will be presented with and without the application of a False Discovery Rate (FDR) correction for multiple testing.

8.3.3. Cumulative costs and cost rates

Cumulative costs will be visualized spanning the baseline and exposure periods via mean cumulative function step curves (with a grey zone corresponding to the 95% confidence interval)(Nelson 1998; 2000; Blackstone and Rajeswaran 2019). A marked increase in the cumulative cost slope is expected at T0, corresponding to the initiation of mepolizumab. However, the cumulative cost slope is hypothesized to later decrease at a currently unknown time point after T0 due to reduced health resource consumption in other sectors and is of interest. The cost rate curve (ie the slope of the mean cumulative cost curve) will be determined by a 28-day sliding window for the demonstration of changes in the speed of accumulating costs. Mean cumulative functions describing the difference between baseline and exposure periods can be computed (Nelson 2000). For the latter, the elapsed time at which the 95% confidence interval no longer contains zero indicates differences in cumulative costs. Similarly, mean cumulative functions for events of interest (specific health resource usages or associated costs found to differ before versus after T0) can be computed.

8.3.4. Potential covariates/subgroups

Subgroups of interest include:

- Demographic groupings: age categories, sex.
- Patients who decrease their consumption of rescue and/or controller medications during the follow-up period versus those who do not.
- Comorbidity groupings: COPD, diabetes

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10. Appendices

Appendix 1: Abbreviations and Trademarks

CEREES: *Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé*; Evaluation committee for research, studies and evaluations in the field of health

CNAMTS: *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés;* French National Health Insurance for Employees

CNIL: Commission Nationale de l'Informatique et des Libertés. The French data protection commission

COPD: chronic obstructive pulmonary disease

CS: corticosteroid

EnCEPP: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance

ICS: inhaled corticosteroid

LABA: long acting beta antagonist

OCS: oral corticosteroid

PDC: proportion of days of follow-up covered by mepolizumab

PMSI: *Programme de Médicalisation des Systèmes d'Information*. A French national hospitalizations database.

SABA: short acting beta antagonist

SNDS : *Système National des Données de Santé.* National Health Data System in France.

SNIRRAM: *Système National d'Information Inter Régimes de l'Assurance Maladie*. The main national claims database in France.

T0: The time of the first mepolizumab administration.

Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

This study will be performed exclusively using French national claims data - Research Not Involving Human Subjects - and corresponds to a standard request for SNDS data access.

In accordance with French regulations, study authorization will be sought with the National Institute of Health Data (*Institut des Données de Santé*), the CEREES (*Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé;* Evaluation committee for research, studies and evaluations in the field of health) and the French data protection commission (*Commission Nationale de l'Informatique et des Libertés*) before commencement. We will also seek ethical approval from the Institutional Review Board at the University Hospitals of Montpellier, Montpellier, France. In addition, the study will be registered prior to data extraction with the following entities: (i) clinicaltrials.gov (public disclosure), (ii) the open science framework (public disclosure), and (iii) www.encepp.eu (European Medicines Agency).

Informed Consent Process

Not applicable.

Data Protection

SNDS data are accessible only by specially trained and qualified individuals.

Publication Policy

- The results of this study may be published or presented at scientific meetings.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Only aggregated statistics (analysis results) will be disseminated. French regulations do not permit re-use or dissemination of the raw data.

1- Data transfer process:
No individual data will be exported from the CNAMTS secured platform. Only the associated/aggregate data and the result tables will be exported from the CNAMTS secured platform.

2- Access to traceability after connections:
CNAMTS will be able to track all connections of qualified people made in the CNAMTS secured platform within the scope of the study.

3- Data preservation:
The project dossier located in the CNAMTS platform will be archived and stored by CNAMTS.
The aggregated data extracted from the analyses and the result tables will be stored for a period of 3 years after the publication of the results, according to the request sent to CNIL.

4- Non-reuse of data:

The investigators will undertake not to reuse the individual data handled in the CNAMTS secured platform outside the scope of the present project.

Data Management

Data-management and analysis will be performed only after favorable opinion from CEREES, authorization from CNIL, and signature of the convention with CNAMTS (*Caisse Nationale d'Assurance Maladie des Travailleurs Salariés;* French National Health Insurance for Employees) to access the SNDS data required for the study.

Data-management and analyses will be performed by authorized and appropriately trained staff at the University Hospitals of Montpellier (Department of Medical Information) to access the data of the SNDS.

Data-management and analyses defined in the protocol will be carried out within a secured platform (SAS® software) from an extraction carried out by CNAMTS. Access to the SNIIRAM data requires therefore an *a priori* definition of a selection algorithm (for e.g. based on based on medication codes UCD 9413850 // code CIP_C13 3400930038352) for patients needed to perform the study and a listing of the variables required.