NON-INTERVENTIONAL STUDY PROTOCOL

Protocol Title:	A multi-country, non-interventional, cohort study to evaluate the effectiveness of OM-85 for the prevention of recurrent respiratory tract infections in paediatric and adult patients, and its use in routine clinical practice
acterProtocol Number:	BV-2023/14
Protocol Version:	Version 2.0
Protocol Date:	22 Nov 2024
Investigational Drug	OM-85
Contract Research Organisation:	Parexel International
Sponsor Contact	PPD
Sponsor Address	OM Pharma SA. Rue du Bois du Lan 22 1217 Meyrin Switzerland
Countries of Study:	China, Belgium, Italy

SIGNATURE PAGE

Sponsor's declaration

Title: A multi-country, non-interventional, cohort study to evaluate the effectiveness of OM-85 for the prevention of recurrent respiratory tract infections in paediatric and adult patients, and its use in routine clinical practice

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This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Society for Pharmacoepidemiology Guidelines on Good Pharmacoepidemiology Practices.

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Date (day month year)

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Billerica, MA, USA

Date (day month year)

Declaration of the Contract Research Organisation

Title: A multi-country, non-interventional, cohort study to evaluate the effectiveness of OM-85 for the prevention of recurrent respiratory tract infections in paediatric and adult patients, and its use in routine clinical practice

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All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol and other scientific data.

The study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee.

The Health Improvement Network (THIN®) data access in Italy and Belgium does not require ethic clearance. However, in case of intended publication of study results, a submission and approval by the THIN Euroboard is mandated. This approval will be obtained before the conduct of the study. No changes will be made to the study protocol without the prior written approval of the Sponsor.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible signatory of the contract research organisation

_____ _____

Name
Title
Institution

Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AIC	Autorizzazione all'Immissione in Commercio
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CCI	CCI
CED	cohort entry date
CI	confidence interval
CCI	CCI
COVID-19	Coronavirus disease 2019
CRO	contract research organisation
EC	ethics committee
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP	general practitioner
GPP	Good Pharmacoepidemiology Practices
ICD-9	International Statistical Classification of Diseases and Related Health Problems 9th Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICS	inhaled corticosteroids
ICU	intensive care unit
IRB	Institutional Review Board
IRR	incidence rate ratio
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LRTI	lower respiratory tract infection
OMOP	Observational Medical Outcomes Partnership
PS	propensity score
PY	person-year
RTI	respiratory tract infection
SAP	statistical analysis plan
SOC	Standard of Care
THIN	The Health Improvement Network
TTE	target trial emulation
URTI	upper respiratory tract infection

RESPONSIBLE PARTIES

Sponsor	OM Pharma SA Rue du Bois du Lan 22 1217 Meyrin Switzerland
Contract Research Organisation	Parexel International 2520 Meridian Parkway, Durham, NC 27713 United States

SYNOPSIS

Protocol Title:	A multi-country, non-interventional, cohort study to evaluate the effectiveness of OM-85 for the prevention of recurrent respiratory tract infections in paediatric and adult patients, and its use in routine clinical practice
Protocol Number:	BV-2023/14
Protocol Version:	Version 2.0
Protocol Date:	22 Nov 2024
Indication	Prevention of recurrent respiratory tract infection
Phase	Non-interventional study
Sponsor:	OM Pharma SA
Study Countries:	Belgium, Italy and China
Rationale and Background:	Respiratory tract infections (RTIs) are a major cause of morbidity, mortality, antibiotic prescriptions, and direct or indirect economic costs, not only in developing countries, but also in industrialised nations. Upper respiratory tract infections (URTIs) have a high cost to society and entail risks of lower respiratory tract involvement, superinfection, and worsening of underlying conditions such as asthma or chronic obstructive pulmonary disease (COPD)/chronic bronchitis (CB). Thus, most exacerbations of asthma and COPD are triggered by RTIs. OM-85 (Broncho-Vaxom®) is an oral medicine which contains an extract of bacterial lysates (21 strains from *Haemophilus influenzae*, *Streptococcus* [*pneumoniae*, *sanguinis*, and *pyogenes*], *Klebsiella pneumoniae* [ssp. *pneumoniae* and ssp. *ozaenae*], *Staphylococcus aureus*, and *Moraxella* [*Branhamella*] *catarrhalis*) which has shown immunomodulating properties both in vitro and in vivo. OM-85 is currently indicated in adults and in children as of 6 months of age for the prophylaxis of recurrent RTIs. OM-85 (7.0 mg) capsules are indicated for use in adults and adolescents above 12 years of age, whereas OM-85 (3.5 mg) capsules and granules in sachets are indicated for use in children from 6 months to 12 years of age. There is an important medical need for further preventive approaches, such as immunomodulators, to improve and regulate innate (non-pathogen specific) immunity in at risk populations with compromised immune function.
Objective(s):	This non-interventional study was designed to investigate the effectiveness of OM-85 and to understand the management of patients with RTIs in routine clinical practice in Belgium, Italy, and China among adult, and paediatric patients with recurrent RTIs (within 24 months prior to cohort entry date [CED] for Inspur; there is no limit for THIN). To investigate effectiveness, RTI patients initiating OM-85 will be compared to RTI patients not initiating OM-85 (standard of care [SOC]/non-user group). The objectives will be studied separately in each study country: Belgium, Italy, and China.

Conducting a summarised analysis combining the results of the countries may be considered in the future.

Primary Objectives:

1. To describe and compare the rate of RTI episodes 12 months before initiating preventive treatment OM-85 and 12 and 24 months after the initiation.
2. To compare the rate of RTI episodes during the follow-up at 12 and 24 months, in patients initiating preventive treatment with OM-85 and in comparable patients not initiating OM-85 (SOC/non-user group).

Secondary Objectives:

1. To describe the baseline characteristics of patients initiating preventive treatment with OM-85 and patients not initiating OM-85 (SOC/non-user group) with respect to demographics, type of previous RTI episodes (URTI, LRTI), comedications, antibiotic use, comorbidities, and number of healthcare visits.
2. To describe the pattern of prescribing OM-85 (e.g., dose, duration, number of cycles) among patients initiating preventive treatment with OM-85 at OM-85 initiation date and in follow-up at 3, 6, 9, 12, and 24 months after initiating OM-85.
3. To describe and compare the rate of RTI episodes 12 months before initiating preventive treatment with OM-85 and 3, 6, and 9 months after the initiation.
4. To compare the rate of RTI episodes during the follow-up at 3, 6, and 9 months in patients initiating preventive treatment with OM-85 and in the patients not initiating OM-85 (SOC/non-user group).
5. To describe the pattern of prescribing specific antibiotics during follow-up at 3, 6, 9, 12, and 24 months, in patients initiating preventive treatment with OM-85 and in patients not initiating OM-85 (SOC/non-user group).
6. To describe the pattern of specific concomitant medications of interest during follow-up at 3, 6, 9, 12, and 24 months, in patients initiating preventive treatment with OM 85 and in patients not initiating OM-85 (SOC/non-user group).
7. To describe overall and RTI episode-specific healthcare visits (general practitioner, specialist care visit, hospital admissions, and emergency department visits) during the 12-month baseline period and during the follow-up at 3, 6, 9, 12, and 24 months in patients initiating preventive treatment with OM-85 and in patients not initiating OM-85 (SOC/non-user group).

Exploratory Objectives

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Overall Design: This is a multi-country, non-interventional cohort study using routinely collected data from healthcare databases to evaluate the effectiveness of OM-85 for the prevention of recurrent RTIs in paediatric and adult patients, and its use in routine practice. The study

was designed to investigate the effectiveness of OM-85 and to understand the management of patients with RTIs in routine clinical practice. The study utilises secondary data from healthcare databases of two European countries (Belgium and Italy, THIN® databases) and China (Inspur database).

The study design was framed using the target trial emulation (TTE) and informed by feasibility assessment. Patients initiating preventive treatment with OM-85 will be compared to patients not initiating OM-85 (SOC/non-user group). Propensity score (PS) matching will be applied to enhance the comparability of the exposure groups (treatment strategies). For patients initiating OM-85, RTI rates will also be compared before and after OM-85 initiation.

The study period will start from the date of earliest data availability and end at the date of latest data availability in each of the data sources. The outcomes will be assessed at 3, 6, 9, 12, and 24 months after the initiation grace period, as per data availability (Belgium, Italy, and China). In each country, the study period will include an inclusion period, a baseline period, an initiation grace period and a follow-up period. These are defined for each included patient:

Inclusion period: The inclusion period will start 12 months after the start of the study period, to enable at least a 12-month baseline period for all included patients. The inclusion period will end 25 months before the end of the study period, to allow a 24-month follow-up time for the last included patient.

CED: The CED is defined as the date of the 2nd, 3rd, … or nth RTI episode during the inclusion period. This is also the date when a patient fulfils all the eligibility criteria. The CED will be selected at random if one patient has several candidate CEDs.

Baseline period: The baseline period for each included patient is defined as the time before the CED. The minimum baseline period will be 12 months, and the maximum baseline period will be 24 months for Inspur, and no limit for THIN (from January 2005 in Belgium, from January 1994 in Italy, and from January 2018 in China).

Initiation grace period: For each included patient, a 30-day initiation grace period starting from the CED will be applied, to allow the included patients to initiate OM-85 during a reasonable period after the CED. Whether the patient initiated treatment during the initiation grace period will determine treatment assignment for the study.

OM-85 initiation date: The OM-85 initiation date will be the date of the first observed prescription of OM-85 at CED or during the 30-day initiation grace period. This is applicable only for the OM-85 exposure group.

Follow-up period: The follow-up for each included patient will start from the end of the 30-day initiation grace period (i.e. 30 days after CED) and will continue until end of the study period or until censoring, whichever occurs first.

Study Population: The overall study population will include patients aged ≥ 1 year of age with ≥1 RTI episodes, and no prescriptions of bacterial lysates within 12 months prior to the inclusion (baseline period). Within the overall study population, patients will be categorised to one of the two exposure groups (treatment strategies): patients who initiated OM-85 at the

	CED or within the 30-day initiation grace period, and SOC/non-user group who did not initiate OM-85 at CED or within the 30-day initiation grace period. Subgroup analysis will be considered; if conducted, several subgroups will be defined for subgroup analyses, such as patients with respiratory comorbidities. Applied stratifications will include those by age groups.
Exposures:	Patients in the overall study population will be categorised to one of the two exposure groups (treatment strategies): patients who initiated OM-85 at the CED or during the 30-day initiation grace period, and SOC/non-user group of patients who did not initiate OM-85 at the CED or during the 30-day initiation grace period.
Data Sources:	THIN is a large European database of fully anonymised, non-linkable and non-extrapolated Electronic Health Records collected at the physicians' level. THIN Belgium covers individual-level patient data from general practitioners (GPs) and has information of > 500,000 patients per year, with an average follow-up of 9 years. THIN Italy covers individual-level patient data from GPs and has information of > 550,000 patients per year, with an average follow-up of 7 years. Inspur is a government-owned company and is authorised to manage city level data in the Tianjin city of China, which is a large city in the North of China. The database includes Electronic Medical Record data at individual-level from 82 public hospitals in Tianjin, including secondary and tertiary hospitals in Tianjin city. Secondary hospitals in China are mid-sized regional facilities with 100 to 500 beds, serving district or county levels, while tertiary hospitals are larger, comprehensive medical centres with over 500 beds, offering more specialised services, advanced technology, and typically serving city, provincial, or national populations.
Data Extraction and Transfer:	THIN will extract the individual-level data from the Italian and Belgian datasets and transfer anonymised individual-level patient data to Parexel for analysis. THIN has built on a common data model, which is mapped to the format of the Observational Medical Outcomes Partnership (OMOP). Data from China will be retrieved from the Inspur database, and subsequent data extraction procedures will be carried out under the supervision of Parexel. The extracted individual-level patient data will then be securely transferred to the local server maintained by Inspur for further analysis by Inspur. Additionally, as part of the data analysis process, Inspur will address any queries or corrections necessary. It is of utmost importance that all amendments made to the data are diligently recorded by Inspur, along with the corresponding dates of these revisions. Inspur will transfer study results as aggregate-level data to Parexel.
Inclusion Criteria:	The overall study population will include patients ≥ 1 year of age, who had ≥ 1 RTI episodes within 12 months prior to CED. Additionally, included patients are required to have ≥ 12 months of continuous enrolment in the database prior to CED, and are not allowed to have a record of any bacterial lysates within 12 months prior to CED.
Exclusion Criteria:	None.

Outcomes:

Primary outcome:

- Primary objectives 1-2: rate of RTI episodes

Secondary outcomes:

- Secondary objective 1: sex, age, Body May Index (BMI), type and number of RTI episodes, comedications, antibiotic prescriptions, comorbidities, healthcare visits
- Secondary objective 2: pattern of prescribing of OM-85
- Secondary objective 3-4: rate of RTI episodes
- Secondary objective 5: pattern of prescribing of antibiotics
- Secondary objective 6: pattern of concomitant medications
- Secondary objective 7: overall and RTI-specific healthcare resource utilisation

Exploratory outcomes:

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Study Size:

All patients available in the databases will be included in the study population. Based on the feasibility assessment, 14,362 patients meeting inclusion criteria and using OM-85 are available in Belgium, 3,219 patients in Italy, and 8,656 patients in China. The study size is based on including the maximum number of patients. However, the strategy to include patients to this study using the TTE framework is not identical to the feasibility assessment, and fewer OM-85 exposed patients will be included in this full study using the TTE framework.

For primary objective 1, the study size required to estimate the difference between rates of two groups (pre- and post- OM-85 treatment) is evaluated based on the level of precision and effect size. With a hypothetical population rate of two episodes per person per year in the baseline and assuming an equal person-time in the two groups (i.e., pre and post treatment), a minimum size of 350 person-years is required to detect a small effect (i.e., an incidence rate ratio of 0.9) with the level of precision where the width of the 95% confidence interval (CI) is no larger than 0.2.No justification of the sample size was performed for the comparative analyses in the primary objective 2.

Data Analysis:

The analyses will be conducted separately in Belgium, Italy and China. Conducting a summarised analysis combining the results of the countries may be considered.

For descriptive statistics, continuous data will be summarised using descriptive statistics (number of non-missing values, mean, median, interquartile range, standard deviation, minimum, and maximum). Categorical data will be summarised using frequency tables

(frequencies and percentages). Time-to-event data will be summarised using the Kaplan-Meier estimate.

From the overall study population, patients will be assigned to the exposure groups (OM-85 or SOC/non-user group) according to whether they received treatment at CED or during the 30-day initiation grace period. Thereafter, PS will be applied to match the OM-85 initiators to comparable SOC/non-user patients, to account for measurable baseline confounding factors between the compared groups. PS of being included in the exposure group initiating OM-85 as opposed to being included in the SOC/non-user group will be estimated for each patient using logistic regression model.

The number and percentage of patients selected into the overall study population, by meeting all the inclusion criteria (no exclusion criteria applied), will be presented for each data source (country) and separated by exposure group. This will be done before and after applying the PS matching (using 1:1 greedy nearest-neighbour method).

The rate of RTI episodes will be estimated by calculating the total number of RTI episodes observed, divided by the total number of person-time (e.g., person-years) during a period of interest. Rates of RTI episodes will be estimated separately in patients initiating preventive treatment with OM-85 and in the SOC/non-user group. Furthermore, rates of RTI episodes during the baseline period will serve as reference in each treatment group to evaluate the effects of therapy during follow-up.

For the comparative analysis comparing the two exposure groups (treatment strategies), generalised linear models with a Poisson distribution or negative binomial distribution (to account for over-dispersion) will be used to estimate the association between the initiation of OM-85 and the outcome of RTI rates, with the natural logarithm of the time at risk in years as offset. Estimated coefficient (i.e., incidence rate ratio) of the exposure variable with corresponding 95% CI and significance level (i.e., p-value) will be reported. For analysis comparing outcomes measured before and after initiating OM-85, cluster-robust standard errors will be estimated to account for correlated data.

AMENDMENTS AND UPDATES

The protocol version 1.0 was finalised on 12 September 2024. Due to the comments received in development of the SAP, the protocol was amended as version 2.0.

Number	Date	Section of study protocol	Amendment or update	Reason
1.0	12 Sep 2024	Original document		
2.0	22 Nov 2024	Sections 3.1, 3.2, 3.3, 3.7, 3.9	1. Using propensity score match only as the main analysis with beginning of follow-up starting at the end of the initiation grace period. The clone censor weighting was included as sensitivity analysis.	1. The clone censor weighting and propensity score matching simultaneously was considered redundant and unnecessary.
		Throughout protocol	2. For clarification >1 RTI during baseline has been updated to ≥ 1 RTI during baseline, which would make the CED the 2^{nd} ,3^{rd} …n^{th} RTI episode.	2. In reviewing the protocol, there was some confusion regarding the number of RTI episodes during baseline for inclusion criteria and how that corresponds to the number RTI episode that is the CED event. Language has been updated for clarification.
		Throughout protocol	3. For objectives where COPD, CB and asthma exacerbations will be examined, it has beene clarified that it is COPD/CB and asthma separately in patients with prior corresponding exacerbations	3. To improve clarity of the objective, wording of the objective has been updated.
		3.2.2.3-Table 5	4. Update age in subpopulations to be ≥65 years and ≥80 years in place of >65 and >80 years	4. To be aligned with the subgroups for age at CED, age groups for subpopulations have been updated.
		Appendix 3	5. Update ICD-10 codes for asthma exacerbation and codes of component conditions in COPD exacerbation	5. In further review of the ICD codes in Appendix 3, additional codes have been found to clarify and expand the definition of asthma exacerbation and some minor modifications to ICD codes in COPD exacerbation, since it was adapted from definitions originally created in ICD-9.

1 ACKGROUND AND RATIONALE

1.1 Background

RTIs are a major cause of morbidity, mortality, antibiotic prescriptions, and direct or indirect economic costs, not only in developing countries, but also in industrialised nations (1–3).

URTIs, i.e., infections of the nose, sinuses, and throat, are the most frequent reason of healthcare solicitation. In high-income countries, where acute RTIs account for about 75% of all antibiotic use (4), URTIs represent the principal cause of unnecessary antibiotic prescriptions in children and adults (5,6). In addition to individual harm, repeated use of antibiotics favours the emergence of drug resistance (7,8). In China, the estimated number of URTIs was 179,077 per 100,000 persons in 2019 (9). URTIs have a high cost to society and entail risks of lower respiratory tract involvement, superinfection, and worsening of underlying conditions such as asthma (10) or COPD (11). Thus, most exacerbations of asthma (12,13) and COPD (14,15) are triggered by RTIs.

LRTIs, i.e., infections of the trachea, bronchi, and lung, are a leading cause of morbidity and mortality worldwide (16,17). Various social and environmental factors, e.g., day-care attendance, air pollution, and parental smoking, increase the number of RTIs in children (18). While LRTIs are less frequent than URTIs, it represents a leading cause of morbidity and mortality, especially in children below 5 years of age (19). In 2019, 185,264 people died in China of LRTIs (9). In 2020, it was reported that 10,409 people died in Belgium and 56,953 people died in Italy due to respiratory diseases (20). Patients with pre-existing respiratory diseases, such as wheezing (21), asthma (22), or COPD (23) have an increased risk of RTIs, which in turn worsen these conditions and draw the patients into a vicious circle.

There is an important medical need for further preventive approaches, such as immunomodulators, to improve and regulate innate (non-pathogen-specific) immunity in at-risk populations with compromised immune function. There are ongoing trends using the potential of immunomodulatory interventions to meet several medical gaps in a vast range of human diseases including in infectious diseases, cancers, autoimmune diseases, and inflammatory conditions. These therapeutics are still under exploration but constitute a perfect tool or an adjunct to regulate some disease progression.

OM-85 (Broncho-Vaxom®) is an oral medicine which contains an extract of bacterial lysates (21 strains from *Haemophilus influenzae*, *Streptococcus* [*pneumoniae*, *sanguinis*, and *pyogenes*], *Klebsiella pneumoniae* [ssp. *pneumoniae* and ssp. *ozaenae*], *Staphylococcus aureus*, and *Moraxella* [*Branhamella*] *catarrhalis*) which has shown immunomodulating properties both in vitro and in vivo. OM-85 is currently indicated in adults and in children as of 6 months of age for the prophylaxis of recurrent RTIs (24). OM-85 (7.0 mg) capsules are indicated for use in adults and adolescents above 12 years of age, whereas OM-85 (3.5 mg) capsules and granules in sachets are indicated for use in children from 6 months to 12 years of age (24).

1.2 Rationale for Study

Several clinical trials have assessed the efficacy of OM-85 in the prevention of respiratory conditions and its safety in paediatric populations (24). However, evidence of the real-world effectiveness in both children and adult populations is limited (25–27). Despite OM-85 having been used in clinical practice for the last 40 years, no multi-country effectiveness study has been conducted in real-world settings. This study will further investigate the effectiveness of OM-85 on the reduction of the rate of RTI episodes and describe the management of RTIs in routine clinical practice in China, Belgium, and Italy with regards to patterns of drug use and healthcare visits, using secondary patient data from healthcare databases.

2 RESEARCH QUESTION AND OBJECTIVES

This non-interventional study was designed to investigate the effectiveness of OM-85 and to understand the management of patients with RTIs in routine clinical practice in Belgium, Italy, and China among adult and paediatric (aged ≥ 1 year) patients with recurrent RTIs (≥ 1 RTI episodes within 12 months before CED). To investigate the effectiveness of OM-85 in patients with recurrent RTIs, RTI patients initiating OM-85 will be compared to RTI patients not initiating OM-85 (SOC/non-user group).

The objectives assessed in this study are described below. The populations included in each of the objectives are described in Section 3.2.2, and outcomes assessed for the objectives in Section 3.3.2. The objectives will be studied separately in each study country: Belgium, Italy, and China. Conducting summarised analysis combining the results of the countries for some of the objectives may be considered in the statistical analysis plan (SAP).

2.1 Primary Objectives

- **Primary objective 1: RTI rate 12 months before and 12 and 24 months after initiating OM-85**: To describe and compare the rate of RTIs episodes 12 months before initiating preventive treatment with OM-85 and 12 and 24 months after the initiation.
- **Primary objective 2: Comparative effectiveness – rate of RTI episodes during follow-up at 12 and 24 months**: To compare the rate of RTI episodes during the follow-up at 12 and 24 months, in patients initiating preventive treatment with OM-85 and in comparable patients not initiating OM-85 (SOC/non-user group).

2.2 Secondary Objectives

- **Secondary objective 1: Patient characteristics at CED**: To describe the baseline characteristics of patients initiating preventive treatment with OM-85 and patients not initiating OM-85 (SOC/non-user group) with respect to demographics, type of previous RTI episodes (URTI, LRTI, Other RTIs), comedications, antibiotic use, comorbidities and number of healthcare visits.

- **Secondary objective 2: Descriptive pattern of prescribing OM-85**: To describe the pattern of prescribing OM-85 (e.g., dose, duration, number of cycles) among patients initiating preventive treatment with OM-85, at OM-85 initiation date and in follow-up at 3, 6, 9, 12 and 24 months after initiating OM-85.
- **Secondary objective 3: RTI rate 12 months before and 3, 6 and 9 months after initiating OM-85**: To describe and compare the rate of RTIs episodes 12 months before initiating preventive treatment OM-85 and 3, 6, and 9 months after the initiation.
- **Secondary objective 4: Comparative effectiveness – rate of RTI episodes during follow-up at 6 and 9 months**: To compare the rate of RTI episodes during the follow-up at 3, 6, and 9 months in patients initiating preventive treatment with OM-85 and in the patients not initiating OM-85 (SOC/non-user group).
- **Secondary objective 5: Descriptive pattern of prescribing antibiotics during follow-up:** To describe the pattern of prescribing specific antibiotics during follow-up at 3, 6, 9, 12, and 24 months, in patients initiating preventive treatment with OM-85 and in patients not initiating OM-85 (SOC/non-user group).
- **Secondary objective 6: Descriptive pattern of concomitant medications of interest during follow-up:** To describe the pattern of specific concomitant medications of interest during follow-up at 3, 6, 9, 12, and 24 months, in patients initiating preventive treatment with OM-85 and in patients not initiating OM-85 (SOC/non-user group).
- **Secondary objective 7: Descriptive healthcare resource utilisation during follow-up:** To describe overall and RTI episode-specific healthcare visits (general practitioner, specialist care visit, hospital admissions, and emergency department visits) at 3, 6, 9, 12, and 24 months in patients initiating preventive treatment with OM-85 and in patients not initiating OM-85 (SOC/non-user group).

2.3 Exploratory Objectives

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3 RESEARCH METHODS

3.1 Study Design

This is a multi-country, non-interventional cohort study using routinely collected data from healthcare databases to evaluate the effectiveness of OM-85 for prevention of recurrent RTIs in paediatric and adult patients, and its use in routine practice. The study utilises secondary data from healthcare databases of two European countries (Belgium and Italy) and China, extracting data from the THIN databases in Belgium and Italy and from the Inspur database in China.

As primary objectives, the effectiveness of OM-85 is assessed through (1) a ***before-after design***, comparing the rate of RTI episodes before and after initiation of OM-85 (primary objective 1), and (2) a ***comparative effectiveness design***, comparing the rate of RTI episodes during follow-up (at 12 and 24 months) between patients who initiated OM-85 and patients who did not initiate OM-85 (primary objective 2).

The patients who did not initiate OM-85 serve as a SOC/non-user comparator group. The secondary objectives include describing the baseline characteristics of patients who initiated OM-85 and the SOC/non-user group, pattern of prescribing OM-85, and patterns of prescribing antibiotics and concomitant medications of interest during follow-up. The objectives will be studied separately in each study country.

The TTE was used as the framework for the design (28,29) of this non-interventional study. The key elements of a hypothetical target trial were defined (eligibility criteria, treatment strategies, treatment assignment, outcomes, follow-up, causal contrasts, and statistical analysis), and the corresponding design elements were defined for this non-interventional cohort study using the healthcare databases (Appendix 6). All elements of the TTE framework are applicable for the comparative effectiveness objectives (primary objective 2, secondary objective 4, and exploratory objectives CCI [redacted]). For the remaining objectives of the study, the elements of the TTE framework utilised include the eligibility criteria to define the study population, treatment strategies to define which exposure groups are investigated, and treatment assignment to define how patients are classified to each treatment strategy (i.e., exposure group).

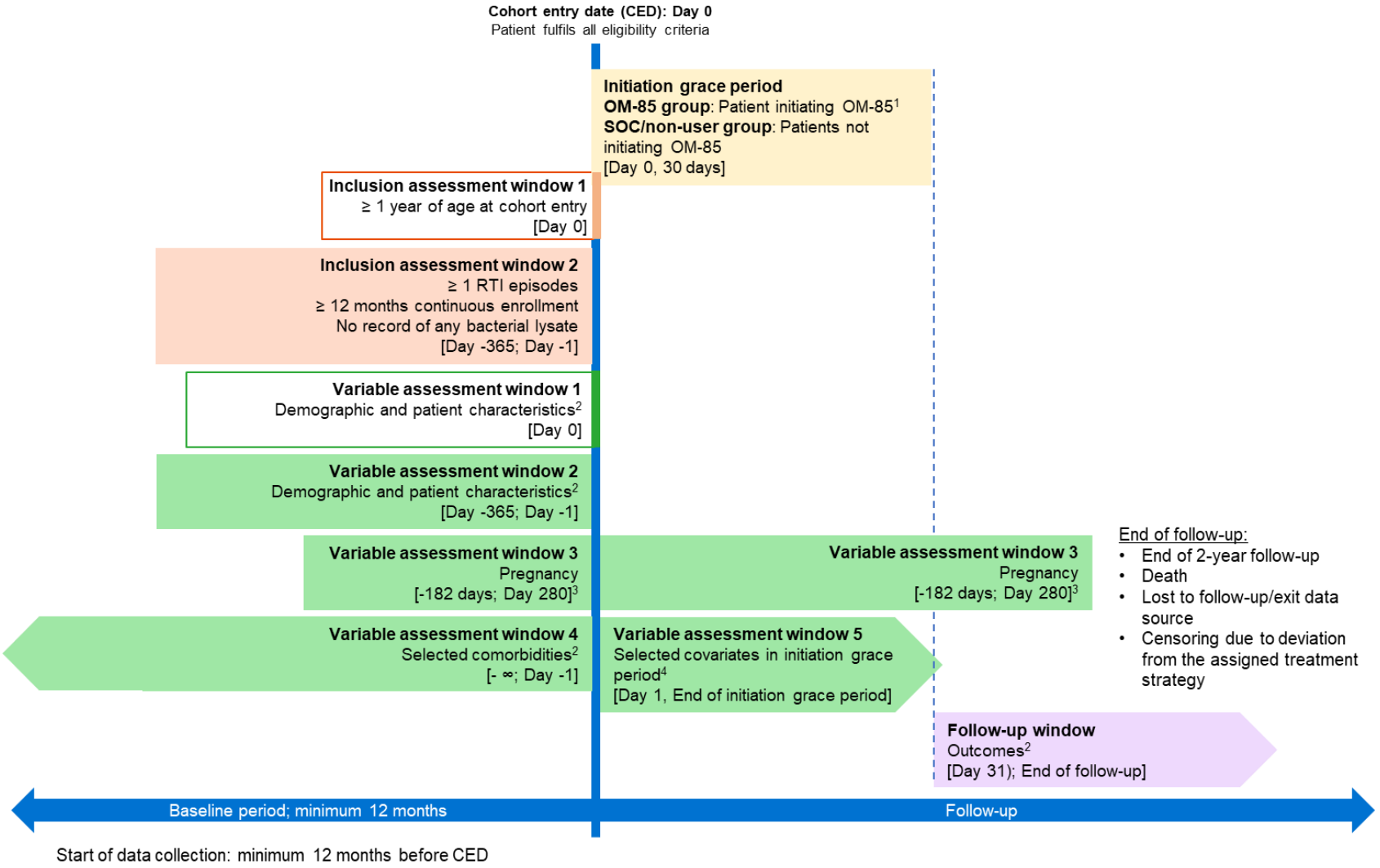
The overall study population will include patients ≥ 1 year of age with ≥ 1 RTI episodes, and no prescriptions of bacterial lysates within 12-months prior to the inclusion (baseline period) (Section 3.2.1). Within the overall study population, patients will be categorised to one of the two exposure groups (treatment strategies): patients who initiated OM-85 at the CED or within 30 days after the CED (i.e. 30-day initiation grace period), and SOC/non-user group who did not initiate OM-85 at CED or within the 30-day initiation grace period (Section 3.3.1).

To emulate randomisation and enhance the comparability of the exposure groups at baseline, the SOC/non-user group will be restricted to patients with similar prognostic factors and probability of receiving OM-85 at CED, by matching on PS.

The study period will start from the date of earliest data availability and end at the date of latest data availability in each of the data sources (Section 3.2.1). The outcomes will be assessed at 3, 6, 9, 12, and 24 months after the CED, as per data availability.

The study design, including time windows for defining key variables, is summarised in Figure 1.

Figure 1 Study Design



Note: CED: cohort entry date; RTI: respiratory tract infection; SOC: standard of care

[1] For the patients who initiate OM-85 during the initiation grace period, another index date is assigned at the date of the 1st OM-85 prescription: OM-85 initiation date. This date is used as the index date in analyses on exclusively OM-85 initiators.

[2] Outcomes defined for each objective are listed in Table 7 and Table 8.

[3] Pregnancy at CED is estimated using a variable assessment window expanding from 183 days (6 months) before CED to 280 days (9 months) after CED, as detailed in Section 3.2.2.3.

[4] Selected covariates are defined during initiation grace period, to be used in sensitivity analysis for clone censor weighting.

period (see Section 3.3.3).

3.1.1 Rationale for the Study Design

Three countries (Belgium, Italy and China) were chosen to have representativeness of routine practice in Europe and China, the two geographical areas of interest. The inclusion of three countries additionally ensures a wide coverage of time, and of different settings of care. Moreover, including three countries increases the total number of patients included in the study.

The use of secondary data from healthcare databases aims to maximise the number of patients included in the analysis. Before starting the study, a robust data source feasibility assessment was carried out to understand the availability of data in the real-world data sources and to assess the suitability of these data sources for examining the study objectives. The robust feasibility involved an assessment of availability of variables of interest, the degree of completeness of key variables, tentative patient count using preliminary inclusion criteria, and operational factors that can affect the conduct of the study.

The study will include patients with recurrent RTIs initiating treatment with OM-85 (new users), to prevent the risk of prevalent user bias (or healthy-user bias). However, no active new user comparator could be identified (Section 3.3.1.1); therefore, the comparator will be a SOC/non-user group. PS matching will be applied to improve the comparability of the exposure groups, where candidate variables for the PS include age, sex, type and number of previous RTI episodes, selected comorbidities, and healthcare visits (Section 3.3.3).

This non-interventional study is designed utilising the TTE framework (28,29), as increasingly recommended in the scientific community (30,31) and by regulators (32), to avoid biases non-interventional studies are prone to, especially time-related biases. Indeed, in this study aligning the CED and treatment initiation is challenging, because treatment initiation cannot be required at CED, as it would lead to very few patients in the OM-85 group. Therefore, the initiation grace period is applied, as recommended in TTE (28,29) and applied in prior studies (33,34). The TTE framework is utilised for the comparative effectiveness objectives, where outcomes in the exposure groups are compared in follow-up. Additionally, the other objectives of the study will be assessed in the same study population and exposure groups, as they are free of time-related biases.

A before-after design among patients initiating OM-85 will also be utilised to provide reference data on differences in study outcomes before and after OM-85 therapy. The minimum of 12 months of baseline data for observing RTIs is secured for each patient.

3.2 Setting

3.2.1 Study Periods

The study periods for each country are summarised in Table 1. The study periods were defined based on the feasibility assessment: in each country, the study period start at the earliest data

availability and ends at the latest date of data availability. The exposure of interest, OM-85, was marketed in these countries throughout the study period.

Table 1 Study Time Periods in Belgium, Italy and China

	Total study period Belgium: January 2005 [1] – July 2024 Italy: January 1994 [2] – July 2024 China: January 2018 [3] – July 2024		
Time before the inclusion period enables a **minimum 12-month baseline period** for the first included patient	**Inclusion period: occurrence of CED** Belgium: January 2006 – June 2022 Italy: January 1995 – June 2022 China: January 2019 – June 2022	**Initiation Grace Period:** A 30-day initiation grace period starting from the CED to allow the included patients to initiate OM-85 during a reasonable period after the CED.	Time after the initiation grace period enables a **24-month follow-up** for the last included patient

Note: CED: cohort entry date

[1] For THIN Belgium, the total study period starts from the first data availability from 2005.

[2] For THIN Italy, the total study period starts from the first availability of the general practice data from 1994 onwards (paediatrician data from 2017).

[3] For INSPUR China, the total study period starts from the first availability of reliable electronic data in the database from 2018 onwards.

In each country, the study period will include an inclusion period, a baseline period, an initiation grace period and a follow-up period. These are defined for each included patient:

- **Inclusion period**: The inclusion period, when patients are included to the study in the respective countries, are described in Table 1. The inclusion period will start at least 12 months after the start of the study period, to enable a 12-month baseline period for all included patients. The inclusion period will end 24 months before the end of the study period, to allow a 24-month follow-up time for the last included patient.
- **CED**: The CED is defined during the inclusion period, as the date of the 2nd, 3rd, … or nth RTI episode during the inclusion period (see inclusion criteria in Section 3.2.2). This is also the date when a patient fulfils all the eligibility criteria. The CED can occur any time during the inclusion period. If a patient meets the eligibility criteria more than once during the inclusion period, and thereby has several candidate CEDs, the CED used in the study will be selected at random, which is one of the unbiased methods of selection of index date (29). The CED defines the end of the baseline period and the start of the initiation grace period for each included patient.

- **Baseline period**: The baseline period for each included patient is defined as the time before the CED. The minimum baseline period will be 12 months, and the maximum baseline period will be as long as data are available in each country (from January 2005 in Belgium, from January 1994, for GPs and 2017 for paediatricians, in Italy, and from January 2018 in China). The minimum baseline period of 12 months will be used for assessing the RTI rate during the baseline period and other baseline variables (Section 3.7.4.1). The maximum baseline period (all available data) will be used for selected variables, such as comorbidities (e.g., allergies, myocardial infarction, and cancer, see Table 8), since these could have occurred earlier but may not have been recorded in the data during the 12-month baseline period. Extending the 12-month baseline period for such variables is expected to improve the accurate classification of them (i.e., decreases the risk of covariate misclassification).
- **Initiation grace period**: For each included patient, a 30-day initiation grace period starting from the CED will be applied, to allow the included patients to initiate OM-85 during a reasonable period after the CED, as it is unrealistic to expect that OM-85 would in clinical practice be prescribed on the date of meeting the eligibility criteria (28,29).
- **OM-85 initiation date**: The OM-85 initiation date will be the date of the first observed prescription of OM-85 during the 30-day initiation grace period, starting from the CED. This is applicable only for the OM-85 exposure group.
- **Follow-up period**: The follow-up for each included patient will start from the end of the 30-day initiation grace period for comparative effectiveness analysis and will continue until end of the study period or until censoring (Table 2), whichever occurs first.
- **Censoring during follow-up**: Patients in the SOC/non-user group are censored at the date of initiating OM-85 (Table 2).

Table 2 Events Ending Follow-up and Censoring Variables

		Operational Definition
Events ending follow-up, throughout the follow-up		
1	End of 24-month follow-up	2 years from end of initiation grace period for each patient
2	Death	For THIN Italy and Belgium: last contact date, which defines exit from the database regardless of reason (death, physician change, or choosing to exit the database) For Inspur China: Date of death directly available by a report from social security sent to Inspur
3	Loss to follow-up/exit of data source	For THIN Italy and Belgium: last contact date, which defines exit from the database regardless of reason (death, physician change, or choosing to exit the database) For Inspur China: Date of lost to follow-up, which defines exit from the database regardless of reason (death or migration to another city)
Censoring during follow-up, after the 30-day initiation grace period: deviation from the assigned treatment strategy		
1.1	OM-85 group: None	-
1.2	SOC/non-user group: at first date of OM-85 prescription during follow-up (after the initiation grace period)	Same
1.3	Sensitivity analysis: The SOC/non-user group are censored at the first date of prescription for any bacterial lysate (including OM-85), the OM-85 group would be censored at the first date of prescription of any bacterial lysate other than OM-85 during follow-up	Same

Note: CED: cohort entry date; SOC: standard of care; THIN: The Health Improvement Network.

3.2.2 Study Population

The overall study population will include patients ≥ 1 year of age with ≥ 1 RTI episodes and no prescriptions of bacterial lysates within 12 months prior to inclusion to the study. Additionally, included patients will be required to have ≥ 12 months of continuous enrolment in the database prior to inclusion. The inclusion criteria are detailed in Table 4, Section 3.2.2.1. No exclusion criteria are applied for this study.

The CED is the date of the 2nd, 3rd, … or nth RTI episode, i.e., the date of fulfilling this inclusion criterion. During the inclusion period, patients can have several CEDs. For patients with several CEDs, the CED of the patient used in the study will be selected randomly, which is one of the unbiased methods to select the date (29). Thus, each patient can enter the study only once.

Patients in the overall study population will be categorised to one of the two exposure groups (treatment strategies): patients who initiated OM-85 at the CED or during the 30-day initiation grace period, and SOC/non-user group of patients who did not initiate OM-85 at the CED or during the 30-day initiation grace period.

The primary and secondary objectives and the exploratory objectives CCI will be studied in the overall study population (Table 3). The exploratory objectives CCI CCI CCI. The sub-populations applied in this study are further described in Section 3.2.2.3.

Table 3 Populations for Each Study Objective

Objective		Population In Which Studied and Index Date
Primary objectives		
1	RTI rate 12 months before and 12 and 24 months after initiating OM-85	• OM-85 initiators only, within the overall study population • Index date: OM-85 initiation date
2	Comparative effectiveness – rate of RTI episodes during follow-up at 12 and 24 months	• Both exposure groups (OM-85 initiators and SOC/non-user group) within the overall study population • Index date: end of initiation grace period
Secondary objectives		
1	Patient characteristics at CED	• Both exposure groups (OM-85 initiators and SOC/non-user group) within the overall study population • Index date: CED
2	Descriptive pattern of prescribing OM-85	• OM-85 initiators only, within overall study population • Index date: OM-85 initiation date
3	RTI rate 12 months before and 6 and 9 months after initiating OM-85	• OM-85 initiators only, within the overall study population

Objective		Population In Which Studied and Index Date
		• Index date: OM-85 initiation date
4	Comparative effectiveness – rate of RTI episodes during follow-up at 6 and 9 months	• Both exposure groups (OM-85 initiators and SOC/non-user group) within the overall study population • Index date: end of initiation grace period
5	Descriptive pattern of prescribing antibiotics during follow-up	• Both exposure groups (OM-85 initiators and SOC/non-user group) within the overall study population • Index date: end of initiation grace period
6	Descriptive pattern of concomitant medications of interest during follow-up	• Both exposure groups (OM-85 initiators and SOC/non-user group) within the overall study population • Index date: end of initiation grace period
7	Descriptive healthcare resource utilisation during follow-up	• Both exposure groups (OM-85 initiators and SOC/non-user group) within the overall study population • Index date: end of initiation grace period
Exploratory objectives		
1	CCI CCI CCI	CCI CCI CCI CCI CCI
2	CCI CCI CCI	CCI CCI CCI CCI CCI CCI
3	CCI CCI CCI	CCI CCI CCI CCI CCI CCI
4	CCI CCI	CCI CCI CCI CCI CCI CCI
5	CCI CCI	CCI CCI CCI CCI CCI CCI

Objective		Population In Which Studied and Index Date
		CCI
6	CCI CCI CCI CCI	CCI CCI CCI
7	CCI CCI CCI CCI	CCI CCI CCI CCI
8	CCI CCI CCI CCI CCI	CCI CCI CCI
9	CCI CCI CCI CCI CCI	CCI CCI CCI CCI
10	CCI CCI CCI CCI	CCI CCI CCI
11	CCI CCI CCI CCI CCI	CCI CCI CCI CCI

Note: CCI; CED: cohort entry date; CCI;
COVID-19: coronavirus disease 2019, RTI: respiratory tract infection; SOC: standard of care.

3.2.2.1 Inclusion Criteria

The inclusion criteria are described in Table 4. Patients will be included into this study only if all the inclusion criteria are met. These inclusion criteria define the overall study population.

Table 4 Inclusion Criteria

	Inclusion Criteria	Operational Definition
1	Patient aged ≥ 1 year of age at CED	Aged ≥ 1 year at CED
2	Patient has ≥1 RTI episodes during the 12-month baseline period prior to CED	≥ 1 RTI episodes within a 12-month period during the inclusion period. The CED is the date of the 2nd, 3rd, … or nth RTI episode (i.e., date of fulfilling the inclusion criteria). If one patient has multiple CED during the inclusion period, the CED will be selected randomly. The definition of an RTI episode provided in Section 3.3.2.1
3	Patient has ≥ 12 months of continuous enrolment in the database prior to CED	≥ 12 months of continuous enrolment in the database prior to the CED. Operationally, patients were required to have entered the database at least 12 months before the CED to be included in the study. In THIN (Belgium and Italy), this can be defined by a district variable for entry to the database: first contact date. In Inspur (China), patients are required to have records in the database at least 12 months before the CED (during the 12-month baseline period) to be eligible for inclusion
4	No record of a prescription of any bacterial lysates in the 12-month baseline period prior to CED	No record of the country-specific drug codes (Appendix 4) during the 12-month baseline period

Note: CED: cohort entry date; RTI: respiratory tract infection; THIN: The Health Improvement Network.

Inclusion criterion 2 on the requirement of having ≥ 1 prior RTI episodes is important to apply because OM-85 is indicated for prevention of recurrent RTIs (24). However, patients in the SOC/non-user comparator group may still have fewer prior recurrent RTIs than the OM-85 group receiving preventive therapy. Therefore, prior recurrent RTIs will also be used in the PS matching of the compared exposure groups. The impact (preventive effect) of OM-85 on the recurrence of RTIs is anticipated to be higher in patients with an increased recurrence risk (35). Hence, the analyses will also be stratified by the number of RTI episodes prior to CED (see Table 5).

The inclusion of patients is not defined by sex. Sex is instead defined at CED and considered in the PS.

3.2.2.2 Exclusion Criteria

No exclusion criteria will be applied.

3.2.2.3 Sub-Populations

In addition to analyses in the overall study populations, the following subgroup analysis will be considered. If conducted, all objectives may be assessed in several sub-populations, including CCI for the exploratory objectives, stratifications, and subgroups of interest (Table 5). Analyses in these sub-populations will be performed only where patient counts allow, considering data protection regulations to mask results if the cell count is small, e.g., < 5 patients.

Table 5 Sub-Populations, Stratifications and Objectives for Which They Are Applied

Sub-Populations	Operational Definition	Objectives In Which Applied
Sub-population of patients who had CCI		
CCI CCI	CCI CCI	• Exploratory objectives CCI only
Stratifications and subgroup considering the CCI		
CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI CCI	• Exploratory objectives CCI only
Other stratifications		
Age at CED: 5 strata • ≥ 1 to < 6 years of age • ≥ 6 to < 12 years of age • ≥ 12 to < 18 years of age • ≥ 18 to < 65 years of age • ≥ 65 years of age	Based on age at CED	• All objectives
Number of RTI episodes prior to CED: 2 strata • ≥ 1 to ≤3 RTI episodes • > 3 RTI episodes	Based on number of RTI episodes during the 12-month baseline period	• All objectives
Subgroups of patients with selected comorbidities at CED		
CCI CCI Patients with allergic rhinitis at CED Patients with atopic dermatitis at CED Patients with food allergy at CED	≥ 1 record of ICD-9/ICD-10 codes defined in Appendix 3, during the maximum baseline period	• All objectives • Additionally stratified by the above 5age categories
Vulnerable populations (subgroups) at CED		
Patients who were estimated to be pregnant at CED	Ongoing pregnancy and delivery/abortion are defined by ICD-9/ICD-10 codes as in Appendix 3. Patients are estimated to have	• All objectives

	been pregnant at CED if they fulfil any of the following definitions: ≥ 1 record of ICD-9/ICD-10 codes for ongoing pregnancy within 6 months before CED AND no record of delivery or abortion within 6 months before CED OR ≥ 1 record of ICD-9/ICD-10 code for ongoing pregnancy at CED or during follow-up, at longest 6 months after CED OR ≥ 1 record of ICD-9/ICD-10 code for abortion at CED or during follow-up, at longest 3 months after CED OR ≥ 1 record of ICD-9/ICD-10 code for delivery at CED or during follow-up, at longest 9 months after CED	
Patients aged ≥ 65 years at CED	Based on age at CED	
Patients aged ≥ 80 years at CED	Based on age at CED	
Patients with immunocompromised conditions at CED	≥ 1 record of ICD-9/ICD-10 codes or ATC codes defined in Appendix 6, during the maximum baseline period or shorter as detailed in Appendix 6	
Subgroups of OM-85 initiators based on OM-85 treatment cycle length and number[3]		
OM-85 initiators, who had • 1 treatment cycle of < 90 days • 1 treatment cycle of 90 days [4] • 1 treatment cycle of > 90 days to ≤ 180 days • 1 treatment cycle of > 180 days • 2 treatment cycles	Defined based on the variables described in Section 3.3.1.2	• Primary objective 1, secondary objective 3

Note: ATC: Anatomical Therapeutic Chemical; CCI ; CED: cohort entry date; CCI CCI ; COVID-19: coronavirus disease 2019; ICD-9: ICD-10: International Statistical Classification of Diseases and Related Health Problems 9th Revision; International Statistical Classification of Diseases and Related Health Problems 10th Revision; RTI: respiratory tract infection.

CCI

CCI

CCI

CCI

CCI The dates provided in Table 5 applies to the Tianjin Province.

[3] While these subgroups are formed based on OM-85 treatment cycle length and number, the analyses shall be reported with caution because patients who had data available for longer (e.g., longer cycle length) may represented a heathier population, as they had survived longer than the ones with shorter length.

[4] If few patients have a treatment cycle length of exactly 90 days, this category may be collapsed with the first category.

3.3 Variables

Exposures, outcomes and other variables used in the study are detailed in this section. Drugs used for definitions of exposure and other variables will be defined using the Anatomical Therapeutic Chemical (ATC) Classification System in THIN Belgium, the Autorizzazione all'Immissione in Commercio (AIC) code in Italy (marketing authorisation code) and brand names in China. Data on drug use represents prescription records only, as no dispensing records are available in THIN Belgium and Italy, and Inspur (China). Diagnoses used for definitions of outcomes and other variables will be defined using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) in China and Belgium, and both ICD-10 and the 9th revision (ICD-9) in Italy, as applied in each country.

To assess whether the data source contains the needed data elements, the variables to be assessed were selected based on the needs of the research objectives of the full study and the comprehensive feasibility assessment was conducted. The data sources were requested to quantify the availability of the data elements in the data source and if additional patient data are accessible from the originating source(s). If either of these criteria were fulfilled, the variable was considered available. The availability of variables was completed for all data sources.

3.3.1 Exposures

To investigate the effectiveness of OM-85 using the TTE framework, the other clinically relevant treatment strategy that OM-85 will be compared to needs be defined, i.e., a treatment strategy that the patients prescribed OM-85 could alternatively have (28,29). This alternative treatment strategy to patients who initiated OM-85 is defined as "not initiating OM-85", which will represent a SOC/non-user group (Table 6).

A 30-day initiation grace period starting from the CED will be applied for each included patient (Section 3.2.1), to allow the included patients to initiate OM-85 during a reasonable period after the CED, as it is unrealistic to expect that OM-85 would in clinical practice be prescribed on the date of meeting the eligibility criteria (28,29). Patients will be ascertained as treated or untreated depending on whether they received a prescription for OM-85 during the grace period.

After the patients have been categorised to one of the treatment strategies during the initiation grace period, the OM-85 treatment strategy will be considered static and no censoring will be applied due to "deviation from the treatment strategy". Censoring at initiation of other treatments for RTI will not be applied, because patients initiating OM-85 are typically prescribed RTI

treatments as part of RTI treatment pathway, including symptomatic measures and/or antibiotics. In other words, patients in clinical practice may be prescribed other treatments in parallel with OM-85. Therefore, censoring at initiation of another therapy would not be a deviation from the OM-85 treatment strategy. Censoring OM-85 at discontinuation will also not be applicable, because OM-85 is not used continuously in clinical practice, but rather as 3-month or 6-month courses (consisting of monthly 10-days treatment periods). Consequently, all patients initiating OM-85 will be followed-up regardless of initiation or parallel use of other therapies.

The frequency of RTI episodes could be impacted by other treatments taken during the follow-up. However, it is likely that most patients co-medicate over the course of RTI episodes, which would lower the magnitude of effect. To address this limitation, the results will be interpreted considering observed other treatments than the index drug during the follow-up period.

In the SOC/non-user group, patients are censored at the date of observing a record of an OM-85 prescription, as the SOC/non-user patients would then deviate from their treatment strategy.

Table 6 Treatment Strategies (Exposure Groups)

OM-85 group	Patients initiating preventive treatment with OM-85	Initiation of OM-85 at CED or 30 days after (during the 30-day initiation grace period), defined at the first observed prescription of OM-85 during this time, using country-specific drug codes (Appendix 4) The patients are “new users”, as no prescriptions of any bacterial lysates are allowed in the 12-month baseline period. Preventive treatment is considered static; no censoring is applied in follow-up at deviation from treatment strategy. In a sensitivity analysis, patients will be censored at date of the first prescription of another bacterial lysate (Section 3.7.7).
SOC/ non-user group	Patients not initiating OM-85	SOC/non-user group: No initiation of OM-85 at CED or 30 days after (during the 30-day initiation grace period). Censoring at first record of OM-85. In a sensitivity analysis, patients will also be censored at date of the first prescription of another bacterial lysate than OM-85 (Section 3.7.7).

Note: CED: cohort entry date; SOC: standard of care.

3.3.1.1 Justification for Comparator Selection (Alternative Treatment Strategy)

The alternative treatment strategy will be a SOC, non-user group, because in clinical practice, there is no alternative drug that would be prescribed instead of OM-85 for the prevention of RTIs. Other bacterial lysates would be an exception; however, those should not be used as the comparator (see below). When there is no clear alternative to the treatment of interest, patients who did not initiate the drug of interest (non-users) can be used as the comparator (36).

Patients treated with other bacterial lysates could have been a suitable comparator group considering the similarity of the indication, on prevention of RTIs, and thereby likely similar

baseline characteristics than OM-85 treated patients (limited confounding by indication). However, because the objective of this study is not to assess within-class effects they were discarded. In addition, the feasibility assessment demonstrated that the low number of patients treated with other bacterial lysates in the countries of interest would not enable a formal, analytical comparison (< 200 patients in Belgium, < 9,000 in Italy and 52 patients in China after applying the preliminary inclusion and exclusion criteria).

The chosen alternative treatment strategy (SOC/non-user group) is heterogeneous and will include a variety of RTI patients in differing disease stages, RTI frequency and severity. To enhance the comparability of the exposure groups at baseline, the SOC/non-user group will be restricted to patients with similar prognostic factors and probability of receiving OM-85 at CED, by matching on the PS.

3.3.1.2 Pattern of Prescribing OM-85 (Secondary Objective 2)

For the OM-85 group, the following will be defined to analyse treatment patterns:

- **OM-85 initiation date**: The OM-85 initiation date will be the date of the first observed prescription of OM-85 at CED or during the 30-day initiation grace period.
- **OM-85 renewal date**: The prescription date for each subsequent OM-85 prescription during the follow-up is an OM-85 renewal date.
- **Prescribed quantity**: Prescribed quantity is defined as the number of units (capsules or sachets) prescribed to the patient at OM-85 initiation and renewal dates.
- **Daily dose**: The dose is assumed to be 1 unit, i.e. capsule or sachet, per day (24), unless if a specific other daily dose is directly available in the database.
- **Prescribed dose**: The strength of the prescribed units, 7 mg or 3.5 mg, is considered the prescribed dose, unless if a specific other prescribed dose is directly available in the database.
- **Prescription duration**: The duration of each prescription is equal to the prescribed quantity (assuming the one unit per day), multiplied by 3 because OM-85 is prescribed in 10-day courses per month). For example, if a patient is prescribed 10 capsules, the duration of the prescription is 30 days. The start of the prescription duration is the OM-85 initiation or the renewed OM-85 prescription's start date (see definition below).
    - **Cumulative prescription duration of overlapping prescriptions**: If the OM-85 renewal date occurs before the previous prescription duration has ended (or at the end date), the durations of both (or more) prescription durations will be summed. For example, if the prescription duration of the first OM-85 prescription at OM-85 initiation date is 30 days (based on 10 prescribed units) and the patient receives another 30-day prescription 20 days after the OM-85 initiation date, the cumulative prescription duration is 60 days from OM-85 initiation date.

- **Renewed OM-85 prescription's start date**: The start date of a renewed prescription, which is defined as the OM-85 renewal date or the end of the (cumulative) prescription duration +1 day, whichever occurs later. For example (the same example as above), if the prescription duration of the first OM-85 prescription at OM-85 initiation date is 30 days (based on 10 prescribed units) and the patient receives another 30-day prescription 20 days after the OM-85 initiation date, the renewed OM-85 prescription's start date is 30 days +1 day, i.e. 31 days after the OM-85 initiation date.

- **Maximum allowable gap between OM-85 prescriptions, to define OM-85 cycles**: An OM-85 cycle is defined to end when no subsequent OM-85 prescription is observed after a maximum allowable gap (in days) since the most recent OM-85 prescription duration has ended. This maximum allowable gap is defined as 30 days after the most recent OM-85 prescription duration has ended. The OM-85 cycle ends at the end of this gap, i.e., 30 days after the most recent OM-85 prescription duration date, if no renewal is observed during this gap. For example, if the most recent prescription duration is 30 days from the renewed OM-85 prescription's start date, the OM-85 cycle ends 60 days after the renewed OM-85 prescription's start date (30-day prescription duration plus 30-day maximum gap), if no new renewal is observed before the end of this 60-day period.
  - **OM-85 cycle duration**: The OM-85 cycle duration is defined as the time between the OM-85 initiation date and the end date of the maximum allowable gap, 90 days in the above example, consisting of the first prescription of 30 days, the subsequent prescription of 30 days, and the 30-day maximum gap.
  - **2nd OM-85 treatment cycle**: If the patient receives a new prescription after the duration of the 1st OM-85 cycle has ended (i.e. after the maximum allowable gap), the date of that prescription is the start date of the 2nd OM-85 treatment cycle. The same above definitions will be applied to this 2nd cycle, as the 1st cycle, with the exception that the start date for the cycle is the start date of the 2nd OM-85 treatment cycle, not the OM-85 initiation date.
  - **Interval between two OM-85 cycles**: The time between the end of the allowable gap of the 1st OM-85 cycle and the start date of the 2nd OM-85 treatment cycle defines the interval between the OM-85 cycles.

The treatment patterns of interest are detailed in Section 3.3.2.2, Table 8.

3.3.2 Outcomes

3.3.2.1 Primary Outcome

The primary outcome is the rate of RTI episodes.

The below definitions of RTI episodes are based on ICD-9/ICD-10 diagnosis codes (as defined in Appendix 3 in Section 8.3) and are sub-categorised as Upper, Lower RTI or Other RTIs-related diagnoses, and Other diagnoses.

Main RTI episode definition

CCI

CCI

CCI

CCI

CCI

CCI

CCI

Hence, with this definition, 14 days is the maximum length of an RTI episode. Sensitivity analyses may be performed with altered maximum length: 7 days and 21 days.

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

Alternative definitions

Alternative RTI outcome definitions will be explored in Step 1 of the analysis using baseline data (Section 3.7.8). Two alternative definitions are utilised:

Alternative 1 – Simple RTI diagnosis code

An RTI episode is comprised of one RTI-related diagnosis. With this definition, each ICD-9/ICD-10 code for an Upper or Lower RTI will be counted as an RTI episode, regardless of the time elapsed between two codes.

Alternative 2 – Complicated RTI episode

A complicated RTI episode is defined as infection-related complications as recorded in GP/primary care, **or** infection-related hospital admission on the date of or within 30 days after consultation/admission for any RTI diagnosis code (URTI, LRTI, or Other RTIs):

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

These definitions were developed in collaboration with medical experts and clinicians who confirmed that the list of RTI diagnosis codes was appropriate and the maximum episode length for the alternative definition was clinically plausible.

CCI

CCI

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3.3.2.2 Secondary and Exploratory Outcomes

The secondary and exploratory outcomes are described in Table 8.

Table 8 Secondary and Exploratory Outcomes

Objective	Outcome	Definition	Measurement
Secondary objective 1 [1]: Baseline characteristics	Sex	• Biological sex	• Dichotomous variable (male/female) • Measurement at CED
	Age	• Age at index date	• Categorical variable (1 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years, ≥ 18 to < 65 years and ≥ 65 years) • Measurement at CED
	BMI	• BMI = weight(kg)/height(m)^2	• Continuous variable • Measurement closest to CED, during the 12-month baseline period
	Type and number of previous RTI episodes	• URTI only (e.g., acute nasopharyngitis, acute sinusitis, acute pharyngitis, acute tonsillitis) • LRTI only (e.g., whooping cough, pneumonia, acute bronchitis) • Other RTIs only: RTI not classified as upper or lower • Combination of URTI, LRTI, and/or Other RTIs	• Categorical variable (diagnosis-related ICD-9/ICD-10 code, Appendix 3) • Continuous variable (number of URTIs, LRTIs, Other RTIs, URTI/LRTI/Other RTIs combined) • Measurement in the 12-month baseline period
	Comedications	• LABA, LAMA, ICS, LABA/ICS, LABA/LAMA, LABA/LAMA/ICS, antiallergic agents, leukotriene receptor antagonists, symptom relievers, systemic corticosteroids, systemic oral corticosteroids, influenza vaccines[1], influenza antivirals defined using country-specific drug codes (ATC, AIC, Other) (Appendix 4)	• Binary variable (yes/no for each class of medication prescribed) • Continuous variable (number of prescriptions, length of treatment in days) • Measurement in the 12-month baseline period
	Antibiotic prescriptions	• Penicillin/beta-lactams, macrolides, cephalosporins, doxycycline, others, defined using country-specific codes (ATC, AIC, Other) (Appendix 4)	• Binary variable (yes/no for each class of medication prescribed) • Continuous variable (number of prescriptions, length of treatment in days) • Measurement in the 12-month baseline period
	Comorbidities	• Smoking status and alcohol use, as recorded in the database	• Binary variable (yes/no)

Objective	Outcome	Definition	Measurement
		• COPD (including CB), chronic lung disease, asthma, immunocompromised conditions, kidney diseases, liver diseases, cancer, malnutrition, food allergy, congenital malformations of the respiratory tract, ischaemic stroke, heart failure, atrial fibrillation, myocardial infarction, coronary heart disease, diabetes, gastro-oesophageal reflux, allergic rhinitis, atopic dermatitis, defined as ≥ 1 record of the ICD-9/ICD-10 codes (Appendix 3)	• Measurement in the 12-month or the maximum baseline period. The maximum baseline period will be used for selected comorbidities that could have occurred earlier but may not be recorded in the data during the 12-month baseline period, such as allergies (allergic rhinitis and food allergy), myocardial infarction and cancer. These will be detailed in the SAP
	Overall and RTI-specific healthcare resource utilisation [2]	• Overall and RTI-specific visits, where RTI-specific visit is defined as a healthcare visit associated with an RTI diagnosis code • Type of healthcare visit: primary care / outpatient care visit, emergency care visit, hospital admission, ICU admission • Number of visits • Length of stay (for hospitalisation and ICU stays)	• Continuous variable (number of visits, length of stay in days) • Measurement in the 12-month baseline period
Secondary objective 2: Prescribing OM-85	Pattern of prescribing of OM-85	• Number of prescriptions of OM-85 • Prescribed dose • OM-85 cycle duration in days • Number of and interval time between treatment cycles	• The variables needed for treatment patterns are defined in Section 3.3.1.2 • Continuous variables (number of prescriptions, prescribed dose, OM-85 cycle duration in days, number of and interval time between treatment cycles) • Categorical variables, e.g., OM-85 cycle duration < 90 days; 90 days, > 90 days to ≤ 180 days, or > 180 days; ≥ 2 treatment cycles • At OM-85 initiation date and thereafter during follow-up at 3, 6, 9, 12, and 24 months

Objective	Outcome	Definition	Measurement
Secondary objectives 3-4: Rates of RTI episodes	RTI episode	• The episode start date is defined as the date of the first observed diagnosis, and the end date is defined as when a different diagnosis code is available, or after 14 days of the first diagnosis • Record of ICD-9/ICD-10 of URTI, LRTI, Other RTIs (Appendix 3)	• Rate of RTI episodes at 12-month baseline and during follow-up at 3, 6, 9, 12, and 24 months • Rate variable
Secondary objective 5: Prescribing antibiotics	Pattern of prescribing of antibiotics	• Penicillin/beta-lactams, macrolides, cephalosporins, doxycycline, others, defined using country-specific codes (ATC, AIC, Other) (Appendix 4Appendix 4)	• Binary variable (Yes/No for each class of medication prescribed) • Continuous variable (number of prescriptions, length of treatment in days) • At 12-month baseline and during follow-up at 3, 6, 9, 12, and 24 months
Secondary objective 6: Concomitant medications of interest	Pattern of concomitant medications of interest	• LABA, LAMA, ICS, LABA/ICS, LABA/LAMA, LABA/LAMA/ICS, anti-allergic agents, leukotriene receptor antagonists, symptom relievers, systemic corticosteroids, systemic oral corticosteroids, influenza vaccines, influenza antivirals • Defined using country-specific codes (ATC, AIC, Other) (Appendix 4)	• Binary variable (Yes/No for each class of medication prescribed) • Continuous variable (number of prescriptions, length of treatment in days) • At 12-month baseline and during follow-up at 3, 6, 9, 12, and 24 months
Secondary objective 7 [2]: Healthcare resource utilisation	Overall and RTI-specific healthcare resource utilisation	• Overall and RTI-specific visits, where RTI-specific visit is defined as a healthcare visit associated with an RTI diagnosis code • Type of healthcare visits: primary care / outpatient care visit, emergency care visit, hospital admission, ICU admission) • Number of visits • Length of stay (for hospitalisation and ICU stays)	• Continuous variables (number of visits, length of stay in days) • During follow-up at 3, 6, 9, 12, and 24 months
Exploratory objectives CCI	CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI CCI	• Exploratory objective CCI CCI CCI CCI CCI • Exploratory objective CCI CCI

Objective	Outcome	Definition	Measurement
			CCI CCI
Exploratory objective [redacted]	CCI CCI CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI CCI CCI	CCI CCI CCI CCI [redacted] CCI
Exploratory objectives CCI	CCI	CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI
Exploratory objective [redacted]	CCI CCI	[redacted] CCI CCI CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI
Exploratory [redacted]	CCI CCI	[redacted] CCI CCI CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI
Exploratory objective [redacted]	CCI CCI CCI	[redacted] CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI
Exploratory objective [redacted]	CCI CCI CCI	[redacted] CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI

Objective	Outcome	Definition	Measurement
Exploratory objective CCI	CCI CCI CCI	CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI
Exploratory objective CCI	CCI CCI CCI	CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI

CCI .

[2] THIN databases (Italy and Belgium) do not cover hospitalisation stays or visits to the ICU or emergency care, while the Inspur database (China) does not cover primary care.

Note: AIC: Autorizzazione all'Immissione in Commercio; ATC: Anatomical Therapeutic Chemical; BMI: body mass index; CB: chronic bronchitis; CED: cohort entry date; COPD: chronic obstructive pulmonary disease; ICD-9: International Statistical Classification of Diseases and Related Health Problems 9th Revision; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; ICS: inhaled corticosteroids; ICU: intensive care unit; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LRTI: lower respiratory tract infection; RTI: respiratory tract infection; SAP: statistical analysis plan; URTI: upper respiratory tract infection.

ICD-9 codes will be provided in the SAP.

3.3.3 Other Variables

Selected baseline variables described under outcomes (Section 3.3.2.2) will be assessed in the Step 1 analysis and will used for controlling for confounding at baseline, through including the selected variables to the PS and matching OM-85 initiators to non-initiators (SOC/non-user group) using the PS. The following baseline variables will be considered in the PS:

- Patient demographics: Age and sex
- BMI
- RTI history, including type (Upper/Lower/Other) and number of previous RTI episodes
- Comedications
- Antibiotic prescriptions
- Selected comorbidities, especially smoking and respiratory conditions, such as asthma, COPD, and CB
- Overall and RTI-specific healthcare resource utilisation, especially duration of RTI-related hospitalisation(s) as a proxy for severity of prior RTIs
- Calendar year of CED

The confounders applied in the PS will be detailed in the SAP.

Variables used for defining sub-populations are described in Section 3.2.2.3.

3.4 Data Sources

The feasibility assessment was conducted to select the most appropriate and fit-for-purpose data sources for this study. The data sources were selected based on the covered geography, the covered settings of care with particular focus on the capture of primary care, the potential numbers of patients available considering preliminary inclusion criteria, coverage and completeness of variables of interest to address the study objectives, as well as operational considerations such as data access process and timelines. The data sources were requested to quantify the availability of the data elements. The availability of variables was completed for all data sources. According to the feasibility assessment, the data sources described below were the most applicable and will therefore be used as data sources in this study. These data sources are used for defining all variables of the study, including inclusion criteria, variables that will end follow-up, sub-populations, exposures, outcomes, and other variables.

3.4.1 The Health Improvement Network: Belgium and Italy

THIN® is a large European database of fully anonymised, non-linkable and non-extrapolated Electronic Health Records collected at the physicians' level. These anonymised patient-level data are obtained from a network of voluntary physicians. In Belgium and Italy, no ethics submission is needed for the current study. An ethics submission to access data from THIN is mandated in case study results will be published. In such case, THIN will submit an ethical application via the THIN Euroboard.

THIN Belgium covers information from GPs and has information on > 500,000 patients per year, with an average follow-up of 9 years. THIN Italy covers information from GPs and has information on > 550,000 patients per year, with an average follow-up of 7 years. The feasibility assessment found that overall, the variables required to address the primary objectives are well captured and of good completeness in both THIN Belgium and THIN Italy, with the exceptions of vaccine administration, lung function tests, and hospitalisation data. Lung function data will therefore not be collected, and vaccination data will be limited to influenza vaccinations. As information is collected from GPs only, the information on healthcare resource utilisation is not complete. Date of birth is captured as year of birth and therefore age in the first year of life cannot be assessed with further granularity than this.

3.4.2 Inspur: China

Inspur is a government-owned company and is authorised to manage city-level data in the Tianjin city of China, which is a large northern city. The database includes Electronic Medical Record (EMR) data, at the patient level, from 82 public hospitals in Tianjin, including secondary and tertiary hospitals in Tianjin city. Secondary hospitals in China are mid-sized regional facilities with 100 to 500 beds, serving district or county levels, while tertiary hospitals are larger, comprehensive medical centres with over 500 beds, offering more specialised services, advanced technology, and typically serving city, provincial, or national populations. Compared to other

databases in China which cover only tertiary hospitals, Inspur collects regional data from secondary and tertiary hospitals, which increases the representativeness of the Chinese population. The database links EMR data, laboratory data and image data, however, the data are not linkable to other sources outside of the Inspur network. It is noteworthy that only one ethics committee (EC)/IRB is needed for the Inspur database rather than needing each hospital's approval, which facilitates the EC/IRB process. Although the time frame covered in Inspur starts from 2005, reliable data electronic collection/coverage spans from January 2018 to latest available data, which were therefore used for the study period time frame. The feasibility assessment found that most of the variables required for the study are captured with good completeness in the Inspur database, with the exceptions of vaccine administration and lung function tests. These data will therefore not be collected and analysed from Inspur as part of this study. Furthermore, the feasibility counts of patients treated with OM-85 revealed that the majority are children under 11 years of age; however, the adult population remains significant in size (utilising preliminary inclusion and exclusion criteria).

3.5 Study Size

In this non-interventional study, all patients available in the databases will be included in the study population. Based on the feasibility assessment, 14,362 patients meeting inclusion criteria and using OM-85 are available in Belgium (of which 10,555 patients aged ≥ 18 years old), 3,219 patients in Italy (of which 2,742 patients aged ≥ 18 years old), and 8,656 patients in China (of which 1,338 patients aged ≥ 18 years old). The study size is based on including the maximum number of patients for the OM-85 group. However, the strategy to include patients to this study using the TTE framework is not identical to the feasibility assessment, and fewer OM-85 exposed patients will be included in this full study using the TTE framework (Section 3.9.5).

For primary objective 1, the study size required to estimate the difference between rates of two groups (pre- and post- OM-85 treatment) is evaluated based on the precision of the point estimate, as described below.

The CI for point estimate of incidence rate ratio (IRR) is calculated as follows (38), where a and b are the counts of events in each group, PT1 and PT2 are the person-time (in person-years [PYs]) in each group, and F is a quantile of the F distribution.

$$\widehat{\text{IRR}}\ \text{CI} = \left(\frac{PT_2}{PT_1}\right)\left(\frac{a}{b+1}\right)\frac{1}{F_{\alpha/2,\ 2(b+1),\ 2a}}\ \text{to}\ \left(\frac{PT_2}{PT_1}\right)\left(\frac{a+1}{b}\right)F_{\alpha/2,\ 2(a+1),\ 2b}$$

With a hypothetical population rate of 2 episodes per person per year in the baseline (based on reported Upper RTI global age-standardised incidence rate of 225,505 per 100,000 person-years, in the Global Burden of Diseases, Injuries, and Risk Factors Study [GBD] 2019 (39)), and assuming equal person-time in the two groups, the width of the 95% CI for the estimated IRR under difference effect sizes and sample sizes are demonstrated in Table 9.

Table 9 Width of 95% CI of estimated IRR by sample sizes and effect sizes

	Sample size in person-years (PY), per exposure group							
Effect size: IRR (ratio a/b)	150 PY	200 PY	250 PY	300 PY	350 PY	400 PY	450 PY	500 PY
0.5	0.202	0.174	0.155	0.141	0.131	0.122	0.115	0.109
0.7	0.254	0.219	0.195	0.178	0.164	0.154	0.145	0.137
0.9	0.304	0.262	0.234	0.213	0.197	0.184	0.173	0.164
1	0.328	0.283	0.253	0.230	0.213	0.199	0.187	0.178

Note: IRR: Incidence rate ratio; PY: person-years

Under the assumptions described above, to have a level of precision where the width of 95% CI is no larger than 0.2, a minimum size of 350 person-year is required to detect a small effect (i.e., a rate ratio of 0.9). A sample size larger than that will further increase the level of precision.

No justification of the sample size was performed for the comparative analyses specified in the primary objective 2 (40).

3.6 Data Management

3.6.1 Data Processing

The data from Belgium, Italy, and China will be processed separately.

THIN will extract the individual-level data from the Italian and Belgian datasets and transfer anonymised individual-level data to Parexel. THIN has built on a common data model, which is mapped to the format of the OMOP. Parexel will process and analyse the individual-level data.

In China, local data protection regulations prevent Parexel from directly accessing and processing individual-level data. Consequently, a local partner, Inspur, will process the individual-level data and conduct the data analysis under Parexel's guidance and supervision. The extracted individual-level data will be securely transferred to a local server maintained by Inspur. Inspur will supervise the data extraction and conduct the data analysis under the supervision of Parexel. As part of the data analysis process, Inspur will address any queries or corrections necessary. It is of utmost importance that all amendments made to the data are diligently recorded by Inspur, along with the corresponding dates of these revisions. Inspur will transfer study results as aggregate-level data to Parexel.

3.6.2 Archiving Study Records

According to International Society for Pharmacoepidemiology Guidelines on Good Pharmacoepidemiology Practices (GPP), the study archive should be maintained for at least 5 years after final report or first publication of study results, whichever comes later. The archive should include all source data. However, as source data extracted from THIN Italy and Belgium will be licenced for 12 months, those will be kept for one year before destruction.

3.7 Data Analysis

A separate SAP will be produced, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final study report.

For analyses conducted by Parexel using THIN data, SAS® version 9.4 or higher (SAS Institute, Cary, NC, US), and R will be used to conduct analyses and generate tables, listings, and figures in a secure environment, unless otherwise specified in the SAP. For analyses conducted by Inspur in China, R will be used to conduct analysis and generate tables, listings, and figures within the Inspur environment.

The analyses will be conducted separately in Belgium, Italy, and China. Conducting a summarised analysis combining the results of the countries for some of the objectives may be considered in the SAP. The appropriateness of combing the results would be considered, including heterogeneity between the databases (41).

3.7.1 General Considerations

For descriptive statistics, continuous data will be summarised using descriptive statistics (number of non-missing values, mean, median, the first quartile, the third quartile, standard deviation [SD], minimum, and maximum). Categorical data will be summarised using frequency tables (frequencies and percentages) among patients with non-missing values.

The number and percentage of missing data will be presented as a separate category for all variables in the descriptive statistics. For the comparative analysis, only observations with complete data will be used. Multiple imputation might be considered for selected variables after the evaluation of missingness. The handling of missing data will be described in more detail in the SAP.

From the overall study population, patients will be assigned to the exposure groups (OM-85 or SOC/non-user group) as detailed in Section 3.3.1. Thereafter, PS will be applied to match the OM-85 initiators to comparable SOC/non-user patients, to account for measurable baseline confounding factors between the compared groups. PS of being included in the exposure group initiating OM-85 as opposed to being included in the SOC/non-user group will be estimated for each patient using logistic regression model. Confounding factors available in the databases will be evaluated for inclusion as covariates in the logistic model, including but not limited to patient demographics, BMI, history of RTI (including upper vs lower), comedications, comorbidities, clinical characteristics, duration of RTI-related hospitalisation(s), and calendar year of CED (see Section 3.3.3; to be detailed in the SAP). Histogram of the PS for both exposure groups will be generated to visually evaluate if there is substantial overlap. Nearest-neighbour matching based on the PS will be used to form pairs of patients from each exposure group that are comparable in baseline confounding factors. The applied matching ratio will be defined in the SAP.

Comparative analysis comparing outcomes measured before and after OM-85 initiation will be performed in all patients assigned to OM-85 exposure group. The distribution of the outcomes measured before and after OM-85 initiation (including various follow-up windows per specified in each objective) will be presented. Generalised linear models will be used, with the flag that indicates before or after OM-85 initiation as the independent variable and the outcome of interest as dependent variable.

Comparative analysis comparing the two exposure groups (treatment strategies, i.e., OM-85, or SOC/non-user) will be performed among the PS-matched samples. The distribution of the outcomes measured in each exposure group and in various follow-up windows as specified in each objective will be presented. Generalised linear models will be used, with the flag that indicates exposure group assignment (i.e., OM-85 or SOC/non-user) as the independent variable and the outcome of interest as dependent variable.

For all the generalised linear models used, distribution and link functions that are appropriate to the type of outcome will be used. Offset will be applied when applicable. Estimated coefficients (or corresponding exponentiated estimates, e.g., IRR) of the independent variables with corresponding 95% CI and significance level (i.e., p-value) will be reported. Cluster-robust standard errors will be used in estimating CI and significance level, to account for correlated data.

3.7.2 Analysis Population(s)

The number and percentage of patients selected into the overall study population, by meeting all the inclusion criteria (no exclusion criteria applied), will be presented for each data source (country), and separated by exposure group. This will be done before and after applying the PS matching.

The analysis populations for each objective are defined in Section 3.2.2.

Of note, when complete case analysis is used to handle missingness, the number of patients contributing to each analysis depends on the availability of the necessary data within the data sources; therefore, the population size may significantly vary between study objectives.

3.7.3 Analysis of Primary Endpoint: RTI Rates (Primary Objectives 1-2, Secondary Objectives 3-4, Exploratory Objectives CCI)

The primary outcome is the rate of RTIs episodes measured during different periods of interest, as specified in the objectives. The rate of RTI episodes will be estimated by calculating the total number of RTI episodes observed, divided by the total number of person-time (e.g., person-years) during a period of interest. Rates of RTI episodes will be estimated separately in patients initiating preventive treatment with OM-85 and in the SOC/non-user group. Furthermore, rates of RTI episodes during the baseline period will serve as reference in each treatment group to evaluate the effects of therapy during follow-up.

Comparative analysis comparing the RTI rates before and after OM-85 initiation, and analysis comparing RTI rates in the two exposure groups will be performed using approaches as described in the General Considerations. Generalised linear models with a Poisson distribution or negative binomial distribution (to account for over-dispersion) will be used to estimate the association between the initiation of OM-85 and the outcome of RTI rates, with the natural logarithm of the time at risk as offset (42).

The analyses will be identical for the exploratory objectives CCI [redacted] CCI [redacted] (Section 3.2.2.3).

3.7.4 Analysis of Other Secondary Endpoint(s)

3.7.4.1 Baseline Characteristics (Secondary Objective 1)

Patient demographics, type of previous RTI episodes (URTI, LRTI, Other), comedications, antibiotic use (number of prescriptions, types, duration of treatment), comorbidities and healthcare resource utilisation during baseline will be described using descriptive statistics appropriate to the variable type.

3.7.4.2 Prescribing Pattern of OM-85, Antibiotics and Concomitant Medications of Interest (Secondary Objectives 2, 5, 6, and Exploratory Objectives CCI)

For prescribing pattern of OM-85, antibiotics, and other concomitant medications of interest, the number of prescriptions and duration of use of medications of interest will be summarised with descriptive statistics as continuous variables. Dosage level of OM-85 prescription will be described as categorical variable. Categorical variables will be summarised using frequency tables (frequencies and percentages).

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3.7.4.3 Healthcare Visits (Secondary Objective 7, and Exploratory Objectives CCI)

The number and proportion of patients with each type of visit will be reported. Among those with each type of visit, total number of visits, and length of hospitalisations (when applicable) will be reported. Annualised rate expressed by person-years will be calculated.

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3.7.5 Analysis of Other Exploratory Endpoints

3.7.5.1 CCI (Exploratory Objectives CCI)

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3.7.5.2 CCI (Exploratory Objective CCI)

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3.7.6 Subgroup Analyses and Stratifications

Planned subgroup analyses and stratifications are described in Section 3.2.2.3 and will be further detailed in the SAP.

3.7.7 Sensitivity Analyses

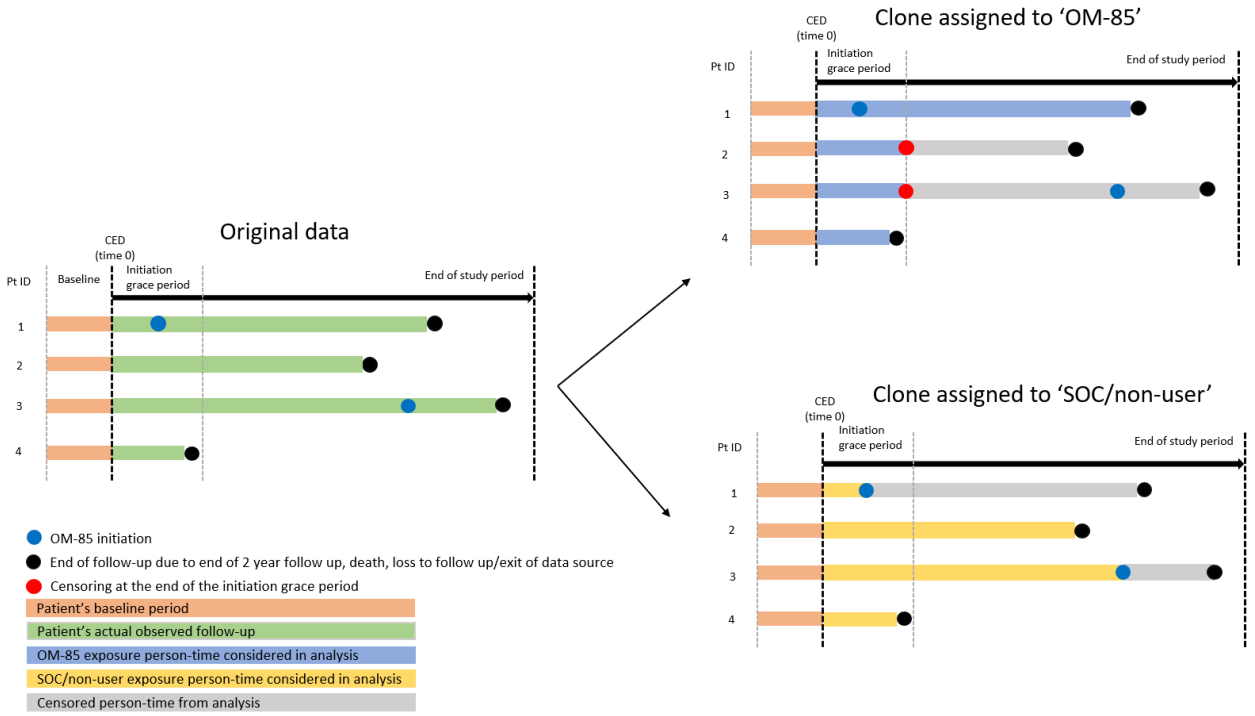
The sensitivity analyses will be applied to primary objectives and will be detailed in the SAP. At minimum, the following will be considered:

- **Varying maximum length of an RTI episode, for primary outcome definition**: The length of an RTI episode (14 days) will be altered in sensitivity analysis using 7 days and 21 days. The results will inform the robustness for the definition in the main analysis.
- **Censoring at initiation of other bacterial lysates than OM-85**: In both exposure groups, patients are censored at date of the first prescription of another bacterial lysate.

In addition, for primary objective 2, sensitivity analysis will be conducted **implementing clone censor weighting methods on the total population to account for potential immortal time bias and selection bias.** In place of PS matching to set up the study cohort, per protocol analysis implementing methods of clone censor weighting will be implemented. In this method, all patients will be included, not only those that are matched in PS matching, and follow-up will begin at CED. To explain further, at CED, each patient will be cloned and assigned to both an exposed and unexposed (one for each clone) and therefore each patient will have been assigned all treatment strategies at CED or time zero of follow-up. Each clone is then followed during the

30-day initiation grace period. Patients will be censored from the cloned OM-85 exposed group at the end of the 30-day initiation grace period, if no prescription of OM-85 is observed by then. Patients will be censored from the cloned SOC/non-user group, if a prescription of OM85 is observed during the 30-day initiation grace period (censoring at the date of the prescription). Artificial censoring of the clones when they deviate from their treatment assignment could create potential selection bias due to informative censoring, and thereby inverse probability weighting will be applied to adjust for potential risk of informative censoring, after the CED. The weights are implemented, because not receiving an OM-85 prescription during the 30-day initiation grace period (and thus being censored) is likely not at random, but influenced by variables that could also impact the outcome (confounders) (37). The censoring weighs up the influence of the patients who remain uncensored to account for similar patients who were censored, breaking the association between censoring and variables that may cause the outcome. The variables included in the weighting can include baseline variables and time-varying confounding variables that could change during the 30-day initiation grace period, such as healthcare resource utilisation (e.g. hospitalisation) or receiving a diagnosis of a respiratory condition. Description of baseline as well time-varying variable that change during the initiation grace period will be described and compared in user and non-user groups. The time-varying variables will be selected from the list of baseline factors (as listed above for PS), but they are measured also after CED. These variables will be further defined in the SAP. The cloning and censoring are illustrated in Figure 3 .

Figure 3 Illustration of Cloning and Censoring the Treatment Strategies



Note: CED: cohort entry date; SOC: standard of care

3.7.8 CCI

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3.8 Quality Control

The study will be conducted according to Parexel's Standard Operating Procedures, and when applicable according to local procedures in each database. The Sponsor may audit Parexel as the contract research organisation (CRO). The process of Parexel supporting Inspur in the data processing is described in Section 3.6.1.

3.9 Limitations of the Research Methods

This is a non-interventional, multi-country study utilising secondary data from healthcare databases. The limitations and potential risks of bias are described below, some of which can be partly minimised at the study design stage, or during data analysis but cannot be fully eliminated due to the observational nature of the study. Despite the limitations, the results of this study will provide important information regarding the effectiveness of OM-85 and generate real-world evidence from a large number of patients. Information obtained from this study will enhance the

general knowledge of OM-85 use and effectiveness among paediatric and adult populations in two geographical areas: Europe and China.

3.9.1 Confounding

As in any non-interventional study without randomisation, the risk of confounding must be considered in the study.

3.9.1.1 Before-After Design Among OM-85 Initiators (Primary Objective 1, Secondary Objective 3, Exploratory Objectives CCI)

In the before-after design, differences in the rates of RTI episodes before and after initiation of OM-85 may be caused by factors other than the OM-85 initiation, factors that differ over the compared time periods. Such factors include progression of the patient's health condition (e.g., COPD), changes in the healthcare system or in access to care (opportunities to detect and record outcomes decrease if access to care decreases), and changes in infection rates in the studied population. Therefore, the results must be interpreted with caution.

3.9.1.2 Objectives Assessed in Both Exposure Groups (Remaining Objectives)

The risk of confounding shall be considered for the objectives that are assessed in both exposure groups:

- Comparative effectiveness design: primary objective 2, secondary objective 4, exploratory objectives CCI
- Descriptive patterns during follow-up in both exposure groups: secondary objectives 5 through 7

In the presence of confounding, the observed results on the outcomes in the compared exposure groups may be due to confounding factors, rather than due to the differing exposure status. Confounding may be a particular challenge in this study, because no active comparator could be identified, as discussed in Section 3.3.1.1.

This risk of confounding will be addressed by matching the compared groups on PS, to emulate randomisation and to enhance the comparability of the exposure groups with regards to their characteristics at CED. Hence, the SOC/non-user group will be restricted to patients with similar prognostic factors and probability of receiving OM-85 during the initiation grace period.

The success of the PS matching (including only measured confounders) will be presented in the descriptive results on baseline characteristics. Similarity of the two exposure groups, i.e., equal distribution of patient characteristics influencing the occurrence of RTI episodes, will relieve uncertainty about the interpretation of the findings. Dissimilarity would warrant cautious interpretations.

As in all non-interventional studies, residual confounding may persist, especially concerning unmeasured confounders (such as lifestyle and health-seeking behaviours), or unknown confounders. Analyses for further addressing confounding analytically and/or investigating the presence of possible confounding (direction and magnitude of anticipated biases) will be considered in the SAP.

It should be noted that for secondary objectives 5-7, on pattern of prescribing antibiotics, concomitant medications of interest, and healthcare resource utilisation, no comparative analyses between the exposure groups will be performed (but may be performed as part of exploratory objectives CCI [redacted]). The descriptive results in both exposure groups separately shall be interested considering possible differences in their baseline characteristics.

3.9.2 Information Bias

Missing or incomplete data in the selected data sources or poor data validity may result in information bias. A feasibility assessment of the data sources was performed before designing the study, which supported the selection of available data with an overall good completeness and validity. Nonetheless, risk of misclassification of variable cannot be ruled out, as described below.

3.9.2.1 Exposure Misclassification

By large, the validity of the exposure assessment from the secondary data sources is expected to be high and risk of misclassification low. According to the conducted feasibility assessment, exposure to both OM-85 and the other bacterial lysates are generally available in the prescribing records of the data sources. However, drugs provided in hospitals are not captured. This possible exposure misclassification is not expected to hamper the result of the study, considering that the patient population is primarily treated in outpatient settings.

This study relies on prescription records, and no data are available regarding if the OM-85 prescription was dispensed to the patient or if the patient actually consumed OM-85. Hence, some patients classified as exposed to OM-85 may not actually have been exposed. This exposure misclassification would likely bias the results towards the null, i.e., the possible protective effect of OM-85 would be more difficult to detect, which shall be considered in the interpretations.

3.9.2.2 Outcome Misclassification/Information Bias

As this is a retrospective study using healthcare databases, diagnosis codes are used to capture RTIs. Based on the feasibility study, diagnosis codes for RTIs are captured in the data sources. Nonetheless, there is a possibility that not all RTI cases are recorded in the data sources, especially since the data sources do not represent all healthcare settings: THIN in Belgium and Italy represents exclusively primary care, and Inspur in China secondary/tertiary care. Overseeing some RTIs would result in underestimating the rate of RTI episodes, which in turn would likely bias towards the null, i.e., the possible protective effect of OM-85 is more difficult to detect, which shall be considered in the interpretations.

In addition, RTI episodes (primary outcome) are not directly available in the data sources, nor are the variables used in trials (43–46) to define RTI episodes. Therefore, RTI episodes are defined based on observed time between records of RTI diagnoses, 14 days (main RTI definition). While this maximum length of an RTI episode was developed in collaboration with clinicians, the duration could lead to underestimating or overestimating the true number of RTIs, which may differ depending on if a patient had mostly URTIs or LRTIs, as well as for children and other ages. The descriptive results on the type of infections recorded in baseline will provide further information on the validity of the time frame of an RTI episode for the study population. Additionally, alternative definitions for RTIs using baseline data will be explored in Step 1 of the analysis, as detailed in Section 3.7.8: a simple and complication RTI definition (Section 3.3.2.1). A sensitivity analyses will also be performed for different lengths of RTI episodes, 7 and 21 days. These will inform about the robustness of the main RTI definition, to be considered in the interpretation of the results.

In the interpretations of the comparative results, the risk of detection or monitoring bias will have to be considered. Namely, the follow-up of the patients who initiate OM-85 may be more intensive than for the patients who did not, or for the same patient before initiating OM-85, as start of a new treatment typically triggers monitoring. This may result in increased ***detection*** of RTIs after initiating OM-85, while corresponding RTIs (especially less severe) could be undetected without an initiation of a new drug and its monitoring. However, considering the safety profile of OM-85, no extensive monitoring is expected. The descriptive results on healthcare resource utilisation will facilitate the interpretation of the results concerning the risk of monitoring bias, potentially increasing the detection of RTIs after initiating OM-85.

The comedications and antibiotic prescription at baseline and treatment patterns in follow-up on OM-85, antibiotics and concomitant medications of interest may be subject to outcome misclassification, because defining patterns of medication use will rely on assumptions. For example, a daily dose for OM-85 (e.g., one capsule per day) has to be defined (if not directly available) to estimate the duration of a prescription, and defining a duration of a treatment episode requires additional assumptions (e.g., maximum allowable gap between prescriptions that defines treatment discontinuation). These definitions are defined for OM-85 in Section 3.3.1.2, will be further detailed in the SAP, and sensitivity analyses may be considered with modified assumptions.

Vaccination status as a baseline variable cannot be assessed for all patients included due to data availability and time since vaccination (e.g., the study design cannot assess early childhood vaccination for elderly patients included in the population due to the maximum baseline period defined in each of the data sources), although it could decrease the number of RTI episodes. Therefore, exclusively vaccines that can be administered yearly, namely the influenza vaccines, are considered in this study for Belgium and Italy only. No vaccine information is available in Inspur (China). Some baseline comorbidities and diagnoses may not be adequately captured during the 12-month baseline period, due to the most recent diagnosis code being recorded

earlier, e.g., COPD being recorded 13 months before the CED. Therefore, the maximum baseline period will be used for assessing the presence of chronic conditions.

3.9.2.3 Misclassification of Other Variables

The classification of patients to subgroups based on diagnosis codes is subject to the same risk of misclassification as mentioned above for comorbidities and diagnoses. The use of the maximum baseline period mitigates this risk. Some of the subgroups were not part of the feasibility assessment, and therefore have a higher risk of misclassification. Specifically, misclassification is expected for food allergy and pregnancy. The subgroup of pregnant women may be over or underestimated, while the subgroup of patients with food allergy will likely be underestimated because some patients with food allergy would not have a corresponding record in the database. These limitations will have to be considered in the interpretation of the results.

3.9.3 Selection Bias

Selection bias refers to the selective inclusion of patients who are not representative of exposure or outcome in the source population, causing distortion in the exposure -outcome relation.

No selection bias is anticipated to emerge from the use of the healthcare databases, which were selected based on a thorough feasibility assessment. While the two European data sources include patients treated in primary care, this type of patients is limited in Inspur (China) where mostly secondary and tertiary care data are available. The combination of the three data sources will provide a wide coverage of the source population in terms of health settings.

Selection bias due to differing settings for the compared exposure groups is not a threat in this study, because both exposure groups are included from the same source populations and time periods, within each country. Further, no selection bias is anticipated to emerge from the application of the inclusion criteria, as availability and data quality of the inclusion criteria in the databases was assessed in the feasibility study.

Further, selection bias is reduced by including in the OM-85 exposure group exclusively patients initiating preventive treatment with OM-85, i.e., new users only, using the 12-month baseline period as a washout when no prescriptions of bacterial lysates are allowed. Including prevalent users (patients with a previous record of OM-85 in the 12-month baseline period) would have two implications:

- Healthy-user or adherer bias, as the included prevalent users would be patients who did not experience early adverse events or lack of early effectiveness.
- The effect against RTI would in reality start before the index date and this effectiveness would not be captured, and therefore the overall effectiveness of OM-85 could be decreased in the results.

By starting follow-up time at the end of the initiation grace period leads to left truncation, however since mortality due to RTI is low, potential for selection bias due to death in the initiation grace period would be low. Furthermore, it is possible that some patients may not match in PS matching; however, given known indications and contra-indications of OM-85, there should be similar patient characteristics in users and non-users and good overlap of PS to create a match. Sensitivity analysis using CCW methods, however, are planned and will use the entire cohort without exclusion and will have follow-up from CED, which will eliminate left truncation.

3.9.4 Time-Related Biases

Time-related biases were minimised by designing the study using the TTE framework (28,29). Importantly, follow-up was carefully selected to start at the end of the initiation grace period, equally for both exposure groups to eliminate immortal time bias. Starting follow-up at OM-85 initiation date for the OM-85 groups, and at CED for the SOC/non-user group would inevitably result in immortal time bias.

The initiation grace period was defined as 30 days, based on alignment with clinicians on a reasonable time for prescribers to prescribe preventive treatment with OM-85 after an RTI. Alternative grace periods may be considered in the SAP.

The time windows to detect the outcomes during the follow-up were chosen based on evidence from interventional studies on OM-85 with up to 12-month follow-up (24). In this study in real-world settings, follow-up was extended to 24 months, with the opportunity to investigate longer-term effectiveness and thereby complement the results of interventional studies. No bias is anticipated from this maximum 24-month window to detect outcomes.

The OM-85 treatment strategy was considered static (Section 3.3.1), based on its clinical use. However, in the static treatment strategy in the main analysis, OM-85 initiators will not be censored if/when they are prescribed other bacterial lysates during the follow-up. While this is consistent with the chosen treatment strategy, the time window for detecting the outcomes associated with OM-85 is not free from the effect of other bacterial lysates. Therefore, censoring follow-up at the first date of a prescription of another bacterial lysate will be applied in a sensitivity analysis, for both exposure groups.

3.9.4.1 CCI [redacted] (Exploratory Objectives CCI [redacted])

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

3.9.5 Risk of Random Error

The precision of the RTI episode rates depends on a range of parameters, including the number of patients included in the study, the average follow-up time available for the patients, and the rate of loss to follow-up. The risk of random error increases and the precision of the rates decreases (i.e., the CIs become wider) with fewer included users of OM-85 and comparator patients, less follow-up time per patient, and/or higher rate of patients lost to follow-up. The risk of random error will be discussed with reporting the results of the study, considering the number of patients included in the analysis and the available follow-up time. However, the data source feasibility assessment showed that the average follow-up time in the selected data sources would allow the analysis at the selected time points with no significant loss to follow-up, which would limit the risk of random error.

At the same time, the strategy to include patients to this study using the TTE framework is not identical to the feasibility study. Specially, the feasibility study did not apply the TTE framework where all patients meeting the inclusion criteria are followed during the initiation grace period, to define in which treatment strategy patients are categorised to. The feasibility study included all patients ever prescribed OM-85 meeting preliminary inclusion and exclusion criteria. In the TTE framework applied here, only patients who initiate OM-85 within 30 days of meeting inclusion criteria (i.e. CED) are included. Additionally, when patients with multiple candidate CEDs will be included to the study population by choosing one CED randomly, there is risk that some OM-85 users will be included to the study as non-users (based on that CED; another CED not selected could be the one leading to OM-85 use). Therefore, fewer OM-85 exposed patients will be included in this full study using the TTE framework. Even though using the TTE framework is a compromise to study size, it minimises bias and improves the internal validity of the study.

4 PROTECTION OF HUMAN SUBJECTS

4.1 Ethical Considerations

The procedures set out in this study protocol are designed to ensure that the Sponsor and CRO abide by the principles of the International Society for Pharmacoepidemiology GPP guidelines (49). The study will also be carried out in compliance with local legal requirements. No ethical approvals are needed for accessing data from Belgium and Italy, unless the results from the THIN databases are intended for publication. For accessing data in China, an ethical approval will be submitted to the ethical committee of the Tianjin main centre in China (Section 3.4).

4.2 Informed Consent

This study utilises exclusively secondary data from data sources collected as part of routine care. Hence, no patient data will be collected for the purpose of this study. For Belgium and Italy, no consent is required as data are anonymised. Patients are informed of the data collection and can choose to exit the database, the non-opposition principle is applied. For China, no consent is

required, as only aggregated data will be disclosed from Inspur to Parexel and the Sponsor. Therefore, informed consent from the participants is not applicable.

4.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and any other relevant documents will be approved by the ethical committee of the Tianjin main centre in China in accordance with local legal requirements. For Belgium and Italy, no protocol approval process is required for the conduct of this study using the THIN databases, as retailed in this protocol. However, in case the results from the THIN databases are intended for publication, a protocol approval of the THIN Euroboard is required. This approval will be obtained before the conduct of the study. The Sponsor must ensure that all ethical and legal requirements have been met before extracting patient data for the study.

To alter the protocol, amendments must be written, with approval from the appropriate personnel, and approval from the ethical committee of the Tianjin main centre in China in accordance with local legal requirements.

Administrative changes may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

4.4 Confidentiality

All study findings and documents will be regarded as confidential. The CRO (Parexel) must not disclose such information without prior written approval from the Sponsor.

The confidentiality of the patients included in the study is ensured by the data holders in the following way. For the THIN databases, all individual-level patient data delivered to the Parexel study team are anonymised, thus preventing re-identification of any individuals in the data. For Inspur, all analysis is carried out by the data holder and only aggregated results are shared with the Parexel study team.

5 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

This study utilises exclusively secondary data from data sources collected as part of routine care. Hence, no patient data will be collected for the purpose of this study. Therefore, management and reporting of adverse events and adverse reactions as part of this study is not applicable.

6 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study will be registered in the EMA-HMA catalogue upon finalisation of the protocol and prior to data access. By signing the study protocol, the Sponsor agrees with the use of results of

the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.

The results obtained within the study are the exclusive property of the Sponsor. The Sponsor recognises the ethical obligation to disseminate findings of potential scientific or public health importance (e.g., results pertaining to the safety of a marketed drug). The study results may be included in abstracts sent to scientific congresses and/or articles sent to scientific reviews. Specific plans for disseminating and communicating the study results will be produced when the results are available.

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8 APPENDICES

8.1 Appendix 1: List of Stand-alone Documents

The following stand-alone documents are available on request.

NA

8.2 Appendix 2: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Checklist for Study Protocols

Study title: A multi-country, non-interventional, cohort study to evaluate the effectiveness of OM-85 for the prevention of recurrent respiratory tract infections in paediatric and adult patients, and its use in routine clinical practice

EMA-HMA Catalogue number: Not yet available
Study Reference Number (If Applicable): Not yet available

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				-
1.1.1 Start of data collection [1]	☐	☒	☐	
1.1.2 End of data collection [2]	☐	☒	☐	
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EMA-HMA catalogue	☐	☒	☐	
1.1.6 Final report of study results	☐	☒	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	2
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	1.2
2.1.2 The objective(s) of the study?	☒	☐	☐	2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	-

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	3.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	3.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	3.3.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	3.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☐	☐	☒	5

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	3.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	3.2.1
	4.2.2 Age and sex	☒	☐	☐	3.2.2
	4.2.3 Country of origin	☒	☐	☐	3.2.1
	4.2.4 Disease/indication	☒	☐	☐	3.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	3.2.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	3.2.2

Comments:

4.2.2: The study population, in terms of eligibility criteria, is not defined based on sex. However, sex is used as a covariate, including as a PS matching variable.

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	3.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	3.9.2.1
5.3	Is exposure categorised according to time windows?	☒	☐	☐	3.3.1.2 / 3.3.2.2

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	3.3.1.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	3.3.1 / 3.3.2.2
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	3.3.1.1

Comments:

5.3: The secondary objective 2 explores the OM-85 exposure patterns based on duration of treatment cycles, which can be used in the interpretation of the comparative results.

5.5: The biological mechanism of action is considered in the construction of the follow-up time, as the exposure is considered static, and not censored when patients end taking daily doses. Additionally, as mentioned above, the secondary objective 2 explores the OM-85 exposure patterns.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	3.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	3.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	3.3.2/ 3.7.8/ 3.9.2.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	-

Comments:

6.3: While no formal validation study is conducted, the primary outcome definition has been designed with clinicians and the main definition is assessed for robustness in Step 1 of the analyses and as part of the sensitivity analyses.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	3.3.3/ 3.7.1/ 3.9.1
7.2 Does the protocol address selection bias? (e.g. healthy-user/adherer bias)	☒	☐	☐	3.1.1/ 3.9.3
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	3.9.2 / 3.9.4

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	3.2.2.3

Comments:

Section 9: Data Sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	3.3 / 3.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	3.3 / 3.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	3.3 / 3.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	3.3 / 3.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	3.3 / 3.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, comedications, lifestyle)	☒	☐	☐	3.3 / 3.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	3.3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	3.3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	3.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	3.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	3.5
10.3	Are descriptive analyses included?	☒	☐	☐	3.7
10.4	Are stratified analyses included?	☒	☐	☐	3.2.2.3 / 3.7.6

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	3.7.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	3.9.2.2
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	3.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	3.7.7

Comments:

10.6: While analytic control of outcome misclassification is included in the protocol, the main definition for the primary outcome is assessed for robustness in Step 1 of the analyses and as part of the sensitivity analyses.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	3.6.2
11.2 Are methods of quality assurance described?	☒	☐	☐	3.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

11.3: While no independent review of study results is in place, the study steering committee will review the results and provide scientific and clinical guidance on interpretations.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	3.9.3
12.1.2 Information bias?	☒	☐	☐	3.9.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	3.9.1
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	3.1.1 / 3.2 / 3.3/ 3.4 / 3.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	4.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	3.2.2.3 / 3.6.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	AMENDMENTS AND UPDATES

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	6
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	6

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

8.3 Appendix 3: International Classification of Disease Codes

Table 10 List of International Statistical Classification of Diseases and Related Health Problems 10th Revision Codes

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
Respiratory Tract Infections (RTIs) – inclusion criterion, primary endpoint and covariate All ICD-10 codes for both upper and lower RTIs will be used to define any RTI		
Upper respiratory tract infections, Upper RTIs (URTIs)		
CCI	PPD	CCI
CCI	PPD	CCI
CCI	PPD	CCI
CCI	PPD	CCI
CCI	PPD	CCI CCI
CCI	PPD	CCI CCI CCI
CCI	PPD	CCI CCI CCI
CCI	PPD	CCI
	PPD	CCI
	PPD	CCI
CCI	PPD	CCI CCI
	PPD	CCI CCI
	PPD	CCI CCI
	PPD	CCI CCI
	PPD	CCI
	PPD	CCI CCI
	PPD	CCI
	PPD	CCI
	PPD	CCI
CCI	PPD	CCI CCI
	PPD	CCI CCI CCI
CCI	PPD	CCI

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
CCI	PPD	CCI CCI CCI
CCI	PPD	CCI
CCI	PPD	CCI CCI
	PPD	CCI
	PPD	CCI
Lower respiratory tract infections, lower RTIs (LRTIs)		
CCI	PPD	CCI
CCI	PPD	CCI CCI
	PPD	CCI
	PPD	CCI CCI
	PPD	CCI CCI
	PPD	CCI CCI
	PPD	CCI CCI CCI
	PPD	CCI CCI
	PPD	CCI CCI
PPD	PPD	CCI
	PPD	CCI CCI
	PPD	CCI CCI
CCI	PPD	CCI
CCI	PPD	CCI CCI
CCI	PPD	CCI CCI
CCI	PPD	CCI
Other RTIs: Respiratory tract infections not classified as upper or lower		
CCI	PPD	CCI CCI CCI
CCI	PPD	CCI CCI

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
CCI [redacted]	PPD	CCI [redacted] CCI [redacted]
CCI [redacted]	PPD	CCI [redacted] CCI [redacted]
Infection-related complications		
Whooping cough	A37	Whooping cough
Scarlet fever	A38	Scarlet Fever
Meningococcal infection	A39	Meningococcal infection
Streptococcal sepsis	A40	Streptococcal sepsis
Other sepsis	A41	Other Sepsis
Other Bacterial diseases, not elsewhere classified	A48	Other Bacterial diseases, not elsewhere classified
Bacterial infection of unspecified site	A49	Bacterial infection of unspecified site
Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere	B95	Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere
Other bacterial agents as the cause of diseases classified elsewhere	B96	Other bacterial agents as the cause of diseases classified elsewhere
Bacterial meningitis, not elsewhere classified	G00	Bacterial meningitis, not elsewhere classified
Meningitis in bacterial diseases classified elsewhere	G01	Meningitis in bacterial diseases classified elsewhere
Encephalitis, myelitis and encephalomyelitis	G04	Encephalitis, myelitis and encephalomyelitis
Eustachian salpingitis and obstruction	H68	Eustachian salpingitis and obstruction
Mastoiditis and related conditions	H70	Mastoiditis and related conditions
Cholesteatoma of middle ear	H71	Cholesteatoma of middle ear
Perforation of tympanic membrane	H72	Perforation of tympanic membrane
Rheumatic fever without mention of heart involvement	I00	Rheumatic fever without mention of heart involvement
Rheumatic fever with heart involvement	I01	Rheumatic fever with heart involvement
Rheumatic chorea	I02	Rheumatic chorea

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
Acute and subacute infective endocarditis	I33	Acute and subacute infective endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	I39	Endocarditis and heart valve disorders in diseases classified elsewhere
Pneumonia due to Streptococcus pneumoniae	J13	Pneumonia due to Streptococcus pneumoniae
Pneumonia due to Haemophilus influenzae	J14	Pneumonia due to Haemophilus influenzae
Bacterial pneumonia, not elsewhere classified	J15	Bacterial pneumonia, not elsewhere classified
Pneumonia due to other infectious organisms, not elsewhere classified	J16	Pneumonia due to other infectious organisms, not elsewhere classified
Pneumonia in diseases classified elsewhere	J17	Pneumonia in diseases classified elsewhere
Pneumonia, organism unspecified	J18	Pneumonia, organism unspecified
Acute bronchitis	J20	Acute bronchitis
Acute bronchiolitis	J21	Acute bronchiolitis
Unspecified acute lower respiratory infection	J22	Unspecified acute lower respiratory infection
Peritonsillar abscess	J36	Peritonsillar abscess
Bronchitis, not specified as acute or chronic	J40	Bronchitis, not specified as acute or chronic
Simple and mucopurulent chronic bronchitis	J41	Simple and mucopurulent chronic bronchitis
Unspecified chronic bronchitis	J42	Unspecified chronic bronchitis
Abscess of lung and mediastinum	J85	Abscess of lung and mediastinum
Pyothorax with fistula	J86	Pyothorax with fistula
Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis (CB)		
Bronchitis	J40	Bronchitis, not specified as acute or chronic
Simple and mucopurulent chronic bronchitis	J41	Simple and mucopurulent chronic bronchitis
Unspecified chronic bronchitis	J42	Unspecified chronic bronchitis
Emphysema	J43	Emphysema
Other chronic obstructive pulmonary disease; including chronic bronchitis (CB)	J44	Other chronic obstructive pulmonary disease

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
Chronic obstructive pulmonary disease exacerbations	See algorithm below	See algorithm below
Chronic lung disease		
Chronic respiratory disease originating in the perinatal period	P27	Chronic respiratory disease originating in the perinatal period
Wilson-Mikity syndrome	P27.0	Wilson-Mikity syndrome
Cystic fibrosis	E84	Cystic fibrosis
Cystic fibrosis with pulmonary manifestations	E84.0	Cystic fibrosis with pulmonary manifestations
Other pulmonary heart diseases	I27	Other pulmonary heart diseases
Coal-worker pneumoconiosis	J60	Coal-worker pneumoconiosis
Pneumoconiosis due to asbestos and other mineral fibres	J61	Pneumoconiosis due to asbestos and other mineral fibres
Pneumoconiosis due to dust containing silica	J62	Pneumoconiosis due to dust containing silica
Pneumoconiosis due to other inorganic dusts	J63	Pneumoconiosis due to other inorganic dusts
Hypersensitivity pneumonitis due to organic dust	J67	Hypersensitivity pneumonitis due to organic dust
Asthma		
Asthma	J45	Asthma
Severe asthma	J46	Status asthmaticus
Asthma exacerbation		
Mild intermittent asthma with (acute) exacerbation	J45.21	Mild intermittent asthma with (acute) exacerbation
Mild persistent asthma with (acute) exacerbation	J45.31	Mild persistent asthma with (acute) exacerbation
Moderate persistent asthma with (acute) exacerbation	J45.41	Moderate persistent asthma with (acute) exacerbation
Severe persistent asthma with (acute) exacerbation	J45.51	Severe persistent asthma with (acute) exacerbation
Unspecified asthma with (acute) exacerbation	J45.91	Unspecified asthma with (acute) exacerbation
Immunocompromised conditions, please see diagnoses used in the definition in Section 8.7		
Kidney diseases		
Essential hypertension	I10	Essential (primary) hypertension

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
Hypertensive heart disease	I11	Hypertensive heart disease
Hypertensive renal disease	I12	Hypertensive renal disease
Hypertensive heart and renal disease	I13	Hypertensive heart and renal disease
Secondary hypertension	I15	Secondary hypertension
Unspecified contracted kidney	N26	Unspecified contracted kidney
Liver diseases		
Alcoholic liver disease	K70	Alcoholic liver disease
Toxic liver disease	K71	Toxic liver disease
Hepatic failure, not elsewhere classified	K72	Hepatic failure, not elsewhere classified
Chronic hepatitis, not elsewhere classified	K73	Chronic hepatitis, not elsewhere classified
Fibrosis and cirrhosis of liver	K74	Fibrosis and cirrhosis of liver
Other inflammatory liver diseases	K75	Other inflammatory liver diseases
Other diseases of liver	K76	Other diseases of liver
Liver disorders in diseases classified elsewhere	K77	Liver disorders in diseases classified elsewhere
Cancer		
Malignant neoplasms	C00 – C97	Malignant neoplasms
In situ neoplasms	D00 – D09	In situ neoplasms
Benign neoplasms	D10 – D36	Benign neoplasms
Neoplasms of uncertain or unknown behaviour	D37 – D48	Neoplasms of uncertain or unknown behaviour
Malnutrition		
Malnutrition	E40 – E46	Malnutrition
Food allergy		
Anaphylactic shock due to adverse food reaction	T78.0	Anaphylactic shock due to adverse food reaction
Other adverse food reactions, not elsewhere classified	T78.1	Other adverse food reactions, not elsewhere classified
Congenital malformations of the respiratory tract		
Congenital malformation of nose	Q30	Congenital malformation of nose

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
Congenital malformation of larynx	Q31	Congenital malformation of larynx
Congenital malformation of trachea and bronchus	Q32	Congenital malformation of trachea and bronchus
Congenital malformation of lung	Q33	Congenital malformation of lung
Congenital malformation of respiratory system	Q34	Congenital malformation of respiratory system
Ischaemic stroke		
Ischaemic stroke	I63	Cerebral infarction
Heart failure		
Heart failure	I50	Heart failure
Atrial fibrillation		
Atrial fibrillation	I48	Atrial fibrillation and flutter
Myocardial infarction		
Myocardial infarction	I21	Acute myocardial infarction
	I22	Subsequent myocardial infarction
	I25	Chronic ischaemic heart disease
Coronary heart disease		
Coronary heart disease	I25	Chronic ischaemic heart disease
Diabetes		
Diabetes	E10 - E14	Diabetes mellitus
Gastro-oesophageal reflux disease		
Gastro-oesophageal reflux disease	K21	Gastro-oesophageal reflux disease
Allergic rhinitis		
Allergic rhinitis	J30	Vasomotor and allergic rhinitis
Atopic dermatitis		
Atopic dermatitis	L20	Atopic dermatitis
Variables used exclusively for subgroups		
Pregnancy (patients who were pregnant)		
Ongoing pregnancy (not yet delivered)	Z32.1	Pregnancy confirmed
	Z33	Pregnant state
	Z34	Supervision of normal pregnancy

Variables: Label For Diseases Used In The Study	ICD-10 Code	ICD-10 Code Label Used in the Study
	Z35	Supervision of high-risk pregnancy
	Z36	Antenatal screening
Delivery	Z37	Outcome of delivery
	Z38	Liveborn infants according to place of birth
Abortion	O03	Spontaneous abortion
	O04	Medical abortion
	O05	Other abortion
	O06	Unspecified abortion

Note: ICD: International Statistical Classification of Diseases and Related Health Problems; SAP: statistical analysis plan; RTI: Respiratory Tract Infection: URTI: Upper RTI; LRTI: Lower RTI; COPD: Chronic Obstructive Pulmonary Disease; CB: Chronic Bronchitis

ICD-9 codes will be provided in the SAP.

8.4 Appendix 4: Anatomical Therapeutic Chemical and Autorizzazione all'Immissione in Commercio Codes

Table 11 List of Anatomical Therapeutic Chemical Codes [1]

Substance Name	ATC Code	ATC Code Label
CCI	PPD	CCI
CCI	PPD	CCI
Comedications		
CCI		
CCI	PPD	CCI
CCI	PPD	CCI CCI
CCI	PPD	CCI CCI
CCI CCI	PPD PPD	CCI CCI CCI CCI CCI CCI
Other medications		
CCI	PPD	CCI
CCI	PPD	CCI
CCI		
CCI	PPD	CCI
CCI	PPD	CCI CCI
CCI	PPD	CCI CCI
CCI CCI	PPD PPD	CCI CCI
CCI		
CCI	PPD	CCI
CCI	PPD	CCI

Substance Name	ATC Code	ATC Code Label
Antibiotics		
CCI	PPD	CCI
CCI	PPD	CCI
CCI	PPD	CCI
CCI	PPD	CCI
CCI	PPD	CCI
CCI	PPD	CCI
Immunocompromised conditions, please see medicines used in the definition in Section 8.7		

Note: ATC: Anatomical Therapeutic Chemical; ICS: inhaled corticosteroids; LABA: long-acting beta-agonists; LAMA: long-acting muscarinic antagonists.

8.5 Appendix 5: Algorithm for Chronic Obstructive Pulmonary Disease Exacerbations

Mapel et al. developed algorithms for identification of moderate and severe COPD exacerbations in two United States healthcare systems using administrative data and electronic medical records (50). The authors validated the algorithms via patient chart review and adjudication by a pulmonologist. These algorithms are presented in Table 12 and will be used to define both moderate and severe COPD exacerbations in the study and will be combined to define acute exacerbations as per study objectives.

Table 12 Algorithm to Identify Chronic Obstructive Pulmonary Disease Exacerbations

Algorithm 1: Moderate Exacerbations	
At least 1 outpatient non-emergency department visit with any of the following ICD-10 codes as the primary diagnosis:	
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
AND at least 1 associated pharmacy dispensing for:	
CCI CCI	PPD
CCI	PPD
CCI CCI	PPD
OR any the following antibiotics (all routes of administration except for topical, ear drops, and eye drops)	
CCI	PPD
CCI	PPD

CCI	PPD PPD
CCI	PPD
CCI	PPD
Algorithm 2: Severe Exacerbations	
At least 1 inpatient hospital stay of two or more days with any of the following ICD-10 diagnosis codes as the primary diagnosis:	
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD
CCI	PPD

Note: ICD: International Statistical Classification of Diseases and Related Health Problems.

Source: Mapel DW, Roberts MH, Sama S, Bobbili PJ, Cheng WY, Duh MS, et al. Development and Validation of a Healthcare Utilisation-Based Algorithm to Identify Acute Exacerbations of Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis. 2021;16:1687–98.

8.6 Appendix 6: Algorithm for Identifying Patients' Immunocompromised Conditions

Immunocompromised Condition	Algorithm Description	ICD-10 Code / ATC Code	ICD-10/ATC Code Label Used in the Study
CCI CCI	CCI CCI CCI CCI CCI CCI CCI	PPD	CCI CCI CCI
		PPD	CCI CCI CCI
		PPD	CCI CCI
CCI CCI CCI	CCI CCI CCI CCI CCI	PPD	CCI
CCI	CCI CCI CCI	PPD	CCI
CCI CCI	CCI CCI CCI CCI CCI CCI CCI CCI CCI	PPD	CCI
		PPD	CCI CCI
		PPD	CCI CCI CCI CCI CCI
		PPD	CCI CCI CCI
		PPD	CCI CCI CCI
		PPD	CCI CCI
		PPD	CCI CCI CCI
		PPD	CCI CCI
CCI CCI CCI	CCI CCI CCI CCI	PPD	CCI
		PPD	CCI CCI CCI

Immunocompromised Condition	Algorithm Description	ICD-10 Code / ATC Code	ICD-10/ATC Code Label Used in the Study
	CCI	PPD	CCI
		PPD	CCI
		PPD	CCI
		PPD	CCI
CCI	CCI	PPD	CCI
		PPD	CCI
		PPD	CCI
		PPD	CCI
		PPD	CCI
CCI	CCI	PPD	CCI
		PPD	CCI
		PPD	CCI
		PPD	CCI
		PPD	CCI
CCI	CCI	PPD	CCI

Immunocompromised Condition	Algorithm Description	ICD-10 Code / ATC Code	ICD-10/ATC Code Label Used in the Study
	CCI		
	CCI	PPD	CCI
			CCI
		PPD	CCI
			CCI
CCI	CCI	PPD	CCI
CCI	CCI		CCI
	CCI		CCI
	CCI		
	CCI		
	CCI		
	CCI		
	CCI		

Note: CED: coding entry date; ICD-10: International Statistical Classification of Diseases and Related Health Problems - 10th Revision; CCI.

8.7 Appendix 7: Target Trial Specification and Emulation

Table 13 Target Trial Specification and Emulation

Protocol component	Target trial specification (hypothetical)	Target trial emulation for a non-interventional (observational) cohort study using healthcare databases	Justifications
Eligibility criteria	**Inclusion criteria** • Aged ≥ 1 year at enrolment • ≥ 1 RTI episodes within 12 months prior to enrolment • No use of any bacterial lysates 12 months prior to enrolment **Exclusion criteria** None.	Same, using the operational definitions for a secondary data. **Inclusion criteria** • Aged ≥ 1 years during the inclusion period • ≥ 1 RTI episodes within a 12-month period during the inclusion period. The CED is the date of the 2nd, 3rd, … or nth RTI episode (i.e., date of fulfilling this inclusion criterion)* • ≥ 12 months of continuous enrolment in the database prior to the CED • No record of prescription of any bacterial lysates within 12-months prior to the CED **Exclusion criteria** None * During the inclusion period, patients can have several CED. For these patients, the CED will be selected randomly, which is one of the unbiased methods to select the date.[1,2] Patients are allowed to enter the study only once.	**Inclusion criteria** • OM-85 is approved from 6 months of age. However, at minimum 12 months of baseline data are needed. Therefore, the minimum age at inclusion is 1 year. • The included patients have to meet the indication for OM-85, to have as comparable exposure groups as possible. Hence, recurrent RTIs have to be an inclusion criterion. • In the non-interventional study, a minimum of 12 months of baseline data are needed for each patient, for defining the inclusion criterion of no use of any bacterial lysates, baseline characteristics, and the rate of RTI episodes before inclusion to the study. This criterion would not be applied in a trial. • Prescriptions of any bacterial lysates is not allowed, in order to include only new users of OM-85 and isolate the effectiveness of OM-85 from other bacterial lysates. Apart from OM-85, other bacterial lysates may have (partially) corresponding effect, and hence included patients will also have to be naïve to them. The term "prescription" is used because the available databases include prescription data. **Exclusion criteria** • No exclusion criteria are defined, because none of the considerations and precautions for OM-85 use described in the product information[3], such as pregnancy or hepatic and renal impairment, are strict contraindications for OM-85.

Protocol component	Target trial specification (hypothetical)	Target trial emulation for a non-interventional (observational) cohort study using healthcare databases	Justifications
Treatment strategies	Randomised to: • OM-85 at enrolment • SOC: No OM-85 at enrolment	One of the following treatment strategies, as observed in real-world clinical practice. • Initiation of OM-85 at CED or during the 30-day initiation grace period • SOC/non-user group: No initiation of OM-85 at during the 30-day initiation grace period	• An initiation grace period of 30 days is defined to allow included patients to initiate OM-85 during a reasonable period, as it is unrealistic to expect that OM-85 would in clinical practice be prescribed on the date of meeting the eligibility criteria. [1, 2] • The alternative treatment strategy is SOC, defined as no initiation of OM-85 (at CED or during the 30-day initiation grace period). In clinical practice, there is no alternative drug that would be prescribed instead of OM-85 for the prevention of RTIs, apart from other bacterial lysates, which however cannot be used as the comparator. When there is no clear alternative to the treatment of interest, patient who did not initiate the drug of interest (non-users) can be used as the comparator.[4] •
Treatment assignment	Individuals are randomly assigned to one of the two treatment strategies. Double-blinded.	Individuals are classified to each treatment strategy, and are assumed to be compatible conditional on selected baseline covariates (confounders). Randomisation is emulated by matching the patients classified to each strategy on PS. Blinding is not possible, and hence patients are aware of the strategy to which they have been assigned.	The PS matching will enhance the comparability of the compared groups at baseline.
Outcomes	**Primary**: RTI episodes **Exploratory**: CCI [redacted] CCI [redacted] CCI [redacted]	Same, using definitions available in secondary databases (see definition in full protocol)	The same definitions as in trials are not available in secondary databases
Follow-up	• Starts at enrolment/ randomisation	Observational analogues: • Starts at end of the grace period	-

Protocol component	Target trial specification (hypothetical)	Target trial emulation for a non-interventional (observational) cohort study using healthcare databases	Justifications
	• 24 months from randomisation, death, or loss to follow-up, whichever occurs first	• End of maximum 24-month follow-up, death, or loss to follow-up/exit of data source, whichever occurs first	
Causal contrasts	Intention-to-treat effect	Observational analogue of per-protocol effect	Intention-to-treat is not possible when the assignment is not known at CED
Statistical analysis	Intention-to-treat analysis	Intention-to-treat [modified] analysis • Treatment assignment will be ascertained according to whether the patient received OM-85 during the initiation grace period. • The SOC/non-user group will be censored at first date of OM-85 prescription during follow-up (after the initiation grace period) • In sensitivity analysis for primary objective 2, clone-censor weighting which is a per-protocol approach will be conducted.	;

Note: CCI [redacted]; CED: cohort entry date; CCI [redacted]; PS: propensity score; SOC: standard of care; RTI: respiratory tract infection.

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