27 October 2022
EMA/761520/2021

# Data analysis plan

## Title: Background incidence rates of Interstitial Lung Disease (ILD)

| Administrative details of the data analysis | |
|---|---|
| Substance(s) | Enfortumab Vedotin / Bosutinib |
| Condition/ADR(s) | Interstitial Lung Disease (ILD) |
| Short title of topic | Background rates of ILD |
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# 1. List of abbreviations

| | |
|---|---|
| *MAH* | *Marketing Authorisation Holder* |
| *EMA* | *European Medicines Agency* |
| *PRAC* | *Pharmacovigilance Risk Assessment Committee* |
| *RDA* | *Rapid Data Analysis* |

# 2. Rationale and background

Interstitial lung disease (ILD) describes a heterogenous group of respiratory disorders affecting the interstitium of the lungs. [1,2] ILD may occur when an injury to the lungs triggers an abnormal healing response. The repair process is disrupted, and the tissue around the alveoli becomes scarred and thickened. Prolonged ILD may result in pulmonary fibrosis, but this is not always the case.

ILD is not a single disease, it encompasses many different pathological processes including drug-induced ILDs. Drug-induced interstitial lung disease (DI-ILD) is also a large and very heterogeneous group of adverse drug reactions, ranging from mild to progressive and life-threatening disease. The number of drugs associated with the development of ILD continues to rise, mainly due to the use of novel monoclonal antibodies and biologics for neoplastic and rheumatologic diseases, many of which are associated with lung toxicity, and includes, among others, chemotherapeutics, molecular targeting agents, immune checkpoint inhibitors, antibiotics, antiarrhythmics, and conventional or biologic disease-modifying antirheumatic drugs. [3]

ILD is usually diagnosed through chest radiography as a first step, but as the chest radiograph can be normal in up to 10% of patients, high resolution computed tomography of the chest is the preferred modality. A lung biopsy can be required if the clinical history and imaging are not clearly suggestive of a specific diagnosis or malignancy cannot otherwise be ruled out.

Treatment of ILD vary depending on the underlying disease. Early identification and discontinuation of the drug are the priority measures if a drug cause is suspected. If a specific occupational exposure cause is identified, the person should avoid that environment. Many cases due to unknown or connective tissue-based causes are treated with corticosteroids.

During routine signal detection, cases of ILD with potential association to Enfortumab Vedotin as well as bosutinib were reported from EudraVigilance and literature. It was proposed to generate background incidence rates of ILD from available a number of European databases in order to support the PRAC assessment.

# 3. Research question and objectives

The objective of the study will be to describe incidence rates of ILD in the general population and stratified by gender, age, and year.

# 4. Research methods

## 4.1. Study design

This will be a cohort study describing incidence rates of ILD in the general population.

## 4.2. Setting and study population

The study population will be the general population (UK) and patients visiting general practices (Germany and France).

## 4.3. Data sources

The following databases will be used: IQVIA™ Medical Research Data (IMRD) UK database, and IQVIA™ Disease Analyzer Germany and France databases. Brief descriptions of these databases are provided in **Annex 1**.

## 4.4. Variables

**Outcomes**: ILDs have been difficult to classify because approximately 180 known individual diseases are characterized by interstitial lung involvement (either primary disease or part of a multiorgan process, e.g., collagen vascular diseases). Therefore, to identify cases that are highly likely to represent the condition of interest, we will follow the **"narrow" scope list of terms** (i.e., very specific preferred terms) documented in the ***Introductory Guide for Standardised MedDRA Queries (SMQs) Version 25.0*** [4].

Detailed list of terms (and their SMQ codes) to be included are shown in **Annex 2**.

We will map these SMQ codes to SNOMED codes, and then find their equivalent to:

- Read codes for IQVIA EMIS UK database
- ICD-10 CODES for IQVIA Germany and France databases

## 4.5. Statistical analysis

### 4.5.1. Main statistical methods

**Incidence rates in the general population:** We will describe the incidence of new onset of ILD diagnoses in patients contributing patient time to the databases listed above. Patients will be required to have a minimum observation time of 365 days prior to entering into each period in order to establish whether events observed during the period are incident (first-ever) cases. Patients will be excluded from the analysis if they had any prior history of the condition in the database.

The **study period** will vary according to the years of coverage in the different databases. For the IMRD UK database, it will be from 2004 to 2021. For the IQVIA™ Disease Analyzer France and Germany databases, the coverage period will be from 2016 to 2020.

- ***Numerator:*** The numerator will consist of the number of patients who experience the event of interest during the yearly time period. Patients with any recorded baseline history of ILD will be excluded, and patients will only be able to contribute one event each.
- ***Denominator:*** The denominator will be defined as patient follow-up time. Patients with a baseline history of ILD at the start of each year will be excluded. Patient follow-up time will be truncated at the occurrence of the first event after which they will not contribute to the analysis.
- ***Analysis:*** Follow-up time will be calculated using the following formula:

  *Follow-up time (years) = (end date for the period – start date for the period + 1) / 365.25*

  Time will be truncated where patients enter or leave the study cohort part way through a time period or where they have an event.

  The **incidence rate** will be then calculated as the number of events divided by the total follow up time:

  *Incidence rate = (number of new onset events) / (total follow up time (years))*

  The incidence will be presented as the number of events per 100,000 person-years and will be calculated for the entire population as well as stratified by:

  - gender,
  - age groups (0-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+), and
  - year

  See **Table shell 1**, which illustrates the estimates that will be provided.

  Confidence intervals around incidence rates will be calculated using exact method for IMRD UK and for IQVIA™ Disease Analyzer Germany and France.

  Analyses will be done using the IHD platform for IMRD UK and IQVIA™ Disease Analyzer France and Germany.

### 4.5.2. Exploratory analysis

Given the broad range of conditions characterised by interstitial lung involvement, we will conduct some additional analyses in which we will explore subgroups of the included conditions, for example, ILDs expected to be a drug-related event or event not stated *versus* others.

### 4.5.3. Sensitivity analysis

None.

### 4.6. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

### 4.7. Limitations of the research methods

It is worth noting that entire patient history may not be included in the data source, and that there is a risk that a prevalent case may have been misclassified as incident (prevalent pool effect). This may result in overestimation of the incidence rate.

Changes in healthcare utilisation during the COVID-19 pandemic (2020-present) might affect routine clinical practices and information recording, therefore possible distortions of the "true" background rates due to potential changes in the way patients interacted with healthcare services in the years 2020 and 2021 versus the previous years will be described.

## 5. Protection of human subjects

Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR) on the protection of individuals.

## 6. Management and reporting of adverse events/adverse reactions

Pursuant to the requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

## 7. Plans for disseminating and communicating study results

The analysis plan and study results will be published in EUPAS registries upon completion.

## 8. References

[1] Kaul B, Cottin V, Collard HR and Valenzuela C (2021) Variability in Global Prevalence of Interstitial Lung Disease. Front. Med. 8:751181.

[2] Pinheiro L, Blake K, Januskiene J, Yue QY, Arlett P. Geographical variation in reporting Interstitial Lung Disease as an adverse drug reaction: findings from an European Medicines Agency analysis of reports in EudraVigilance. Pharmacoepidemiol Drug Saf. 2016 Jun;25(6):705-12.

[3] Spagnolo P, Bonniaud P, Rossi G, et al. Drug-induced interstitial lung disease. Eur Respir J 2022; in press (https://doi.org/10.1183/13993003.02776-2021).

[4] MedDRA®. Introductory guide version 25.0. March, 2022.

**Table shell 1.** Incidence of new onset interstitial lung disease (ILD)* in the general population per 100,000 years of follow-up between 2004 and 2021 overall, and by gender, age group, and year

| | IQVIA EMIS UK | | | | IQVIA Germany | | | | IQVIA France | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Background rates | | | | Background rates | | | | Background rates | | | |
| | Years of follow-up | No. of outcomes | IR per 100,000 person-years | 95% CI | Years of follow-up | No. of outcomes | IR per 100,000 person-years | 95% CI | Years of follow-up | No. of outcomes | IR per 100,000 person-years | 95% CI |
| Overall | | | | | | | | | | | | |
| Gender | | | | | | | | | | | | |
| Male | | | | | | | | | | | | |
| Female | | | | | | | | | | | | |
| Age group (in years) | | | | | | | | | | | | |
| 0-19 | | | | | | | | | | | | |
| 20-29 | | | | | | | | | | | | |
| … | | | | | | | | | | | | |
| 80+ | | | | | | | | | | | | |
| Year | | | | | | | | | | | | |
| 2016 | | | | | | | | | | | | |
| 2017 | | | | | | | | | | | | |
| … | | | | | | | | | | | | |
| 2020 | | | | | | | | | | | | |

* ILD was defined according to Read codes and ICD-10 codes listed in Annex 2. IR= incidence rate; 95% CI confidence interval for incidence rate.

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# Annexes

# Annex 1 - Information on Databases and Healthcare systems included

**IQVIA™ Medical Research Data UK**

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

**IQVIA™ Disease Analyser Germany**

IQVIA™ Disease Analyser Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

**IQVIA™ Disease Analyzer France**

IQVIA™ Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IQVIA™ Disease Analyzer France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS® France and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

# Annex 2 – Codelists

| Preferred term | SMQ codes |
|---|---|
| Acute interstitial pneumonitis | 10066728 |
| Alveolar lung disease | 10073344 |
| Alveolar proteinosis | 10001881 |
| Alveolitis | 10001889 |
| Alveolitis necrotising | 10050343 |
| Autoimmune lung disease | 10080701 |
| Bronchiolitis | 10006448 |
| Bronchiolitis obliterans syndrome | 10083303 |
| Chronic graft versus host disease in lung | 10086041 |
| Combined pulmonary fibrosis and emphysema | 10076515 |
| Confirmed e-cigarette or vaping product use associated lung injury | 10085189 |
| Diffuse alveolar damage | 10060902 |
| Eosinophilia myalgia syndrome | 10014952 |
| Eosinophilic granulomatosis with polyangiitis | 10078117 |
| Eosinophilic pneumonia | 10014962 |
| Eosinophilic pneumonia acute | 10052832 |
| Eosinophilic pneumonia chronic | 10052833 |
| Hypersensitivity pneumonitis | 10081988 |
| Idiopathic interstitial pneumonia | 10078268 |
| Idiopathic pneumonia syndrome | 10063725 |
| Idiopathic pulmonary fibrosis | 10021240 |
| Immune-mediated lung disease | 10085352 |
| Interstitial lung abnormality | 10087834 |
| Interstitial lung disease | 10022611 |
| Low lung compliance | 10086117 |
| Lung infiltration | 10025102 |
| Lung opacity | 10081792 |
| Necrotising bronchiolitis | 10070831 |
| Obliterative bronchiolitis | 10029888 |
| Pleuroparenchymal fibroelastosis | 10084305 |
| Pneumonitis | 10035742 |
| Probable e-cigarette or vaping product use associated lung injury | 10085188 |
| Progressive massive fibrosis | 10036805 |
| Pulmonary fibrosis | 10037383 |
| Pulmonary necrosis | 10058824 |
| Pulmonary radiation injury | 10061473 |
| Pulmonary toxicity | 10061924 |
| Pulmonary vasculitis | 10037457 |
| Radiation alveolitis | 10037754 |
| Radiation bronchitis | 10085628 |
| Radiation fibrosis - lung | 10037758 |
| Radiation pneumonitis | 10037765 |
| Rheumatoid arthritis-associated interstitial lung disease | 10085517 |
| Small airways disease | 10080547 |
| Transfusion-related acute lung injury | 10052235 |