Ocrelizumab: Multi-regional, long-term PASS for MS using mixed data sources

Operational aspects and methods of working with secondary data to address key challenges throughout the process

Laura Girardat-Rotar, Associate Principal, Medical Evidence Practice

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Basel Epidemiology Seminar

Agenda

+ **Introduction to Ocrelizumab PASS**
+ Data source and data flow
+ Study design and analytical approach
+ Learnings and Impact

Information included in the slides related to Ocrelizumab PASS are available in the public arena and aligned with Roche team to speak at the BES.
Study is funded by Roche

IQVIA are supporting Roche in conducting a post-authorisation safety study (PASS) for ocrelizumab

The goal of a PASS is to obtain further information on a medicine's safety, or to measure the effectiveness of risk minimization measures.

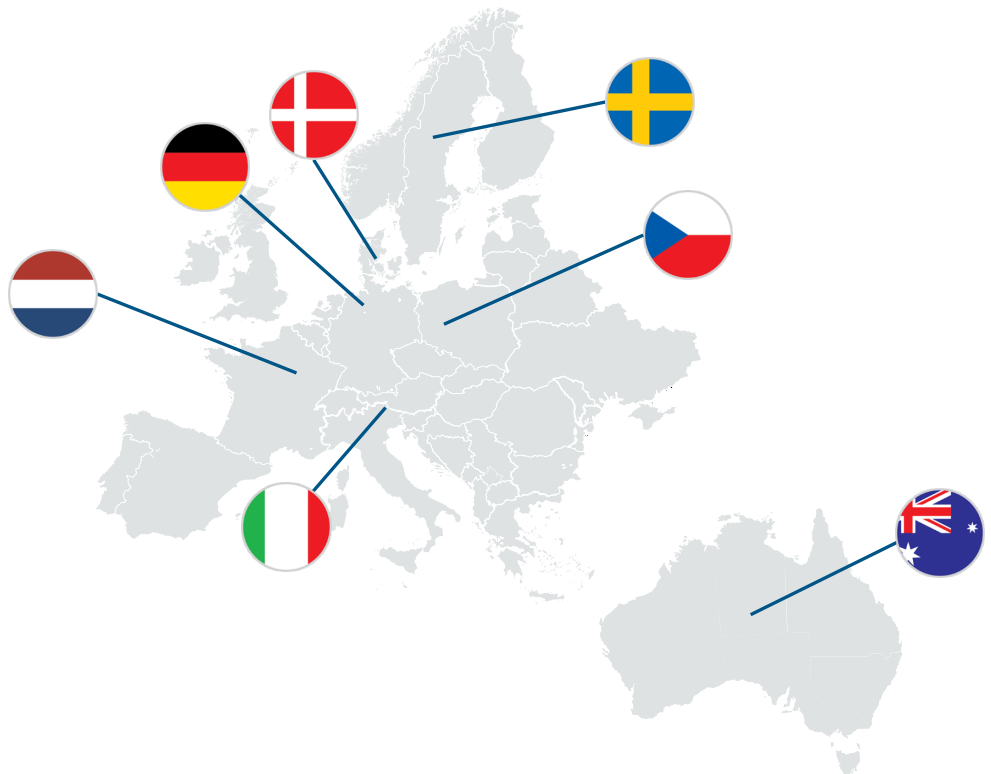
Context

- As part of post-approval risk management plan, Roche is conducting post-marketing safety studies to further characterize the **safety profile of ocrelizumab** in patients with multiple sclerosis (MS)
- MANUSCRIPT (EUPAS28619) has been **approved by the EMA** and investigates **serious adverse** events (SAEs), **malignancy,** and **serious infections following ocrelizumab** treatment in patients with MS in the real-world setting (1, 2).
- This is **one of several post-marketing safety studies**, e.g., the VERISMO (FDA) study (3)

Solution

- **Study objectives** include exploring the rates of malignancies and serious infections, among MS patients treated with ocrelizumab in clinical practice.
- **Multi-country, long-term, observational, mixed data source study** using tailored and unique data flow combining primary data (NIS) and aggregated secondary data from 5 registries
- **Follow-up of for 10 years; treatment (Ocrelizumab) and comparator cohorts** (Disease Modifying Treatment(DMT)).

Geographical scope



References: 1. Protocol BA39730 ocrelizumab Final v1_approved_Redacted.pdf (europa.eu); 2. D Wormser,et al. EAN 2019, Poster EPO3217; 3. Wormser D, et al. AAN 2019;Poster P4.2-043
EMA: European Medicines Agency; DMT: Disease Modifying Therapies, MS: Multiple Sclerosis; FDA: Food and Drug Administration

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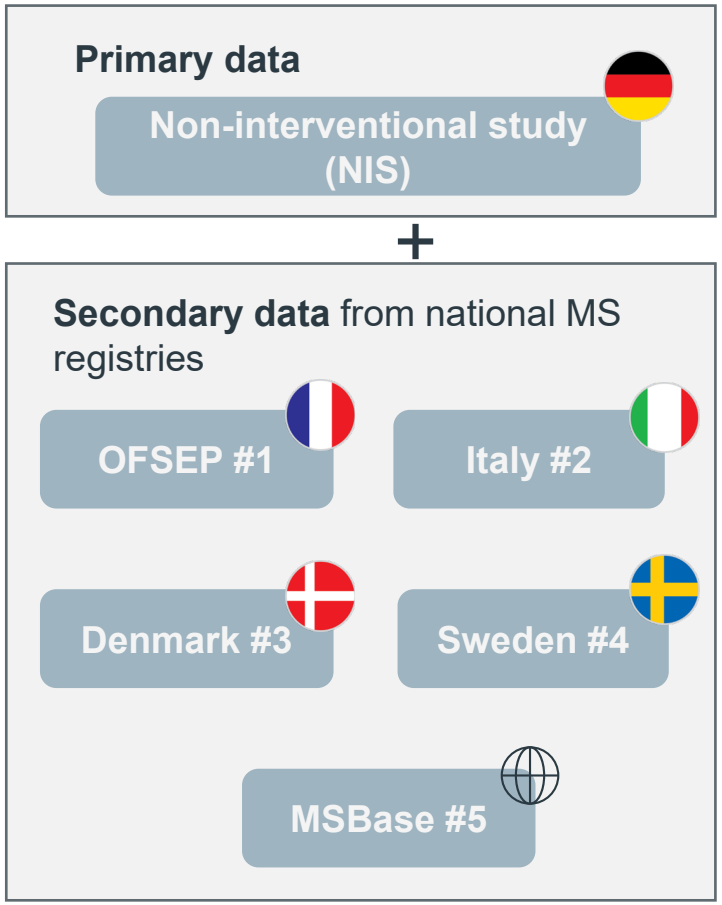
A combination of primary data (NIS) and aggregated secondary data from 5 registries have been selected for the PASS

Selected data sources for PASS



Considerations for assessing data sources in rare disease

Counts for the target patient population including **subpopulations:** Data sources may have **low patient counts in the treatment group.** This may be mitigated by first **forecasting the countries with highest expected users**, or second by expanding the **geographic scope**

Availability of core data elements, origin of data, and possibility of data enhancement: Data sources may **have the capacity to enhance key data variables** (i.e., outcomes and endpoints), such as through Natural Language Processing (NLP) to extract data from physicians' notes

Quality of data, including assessing the completeness and consistency of data and evaluating for bias and confounding. Data sources must be able to demonstrate **that the exposures, outcomes, and covariates are valid and reliable**.

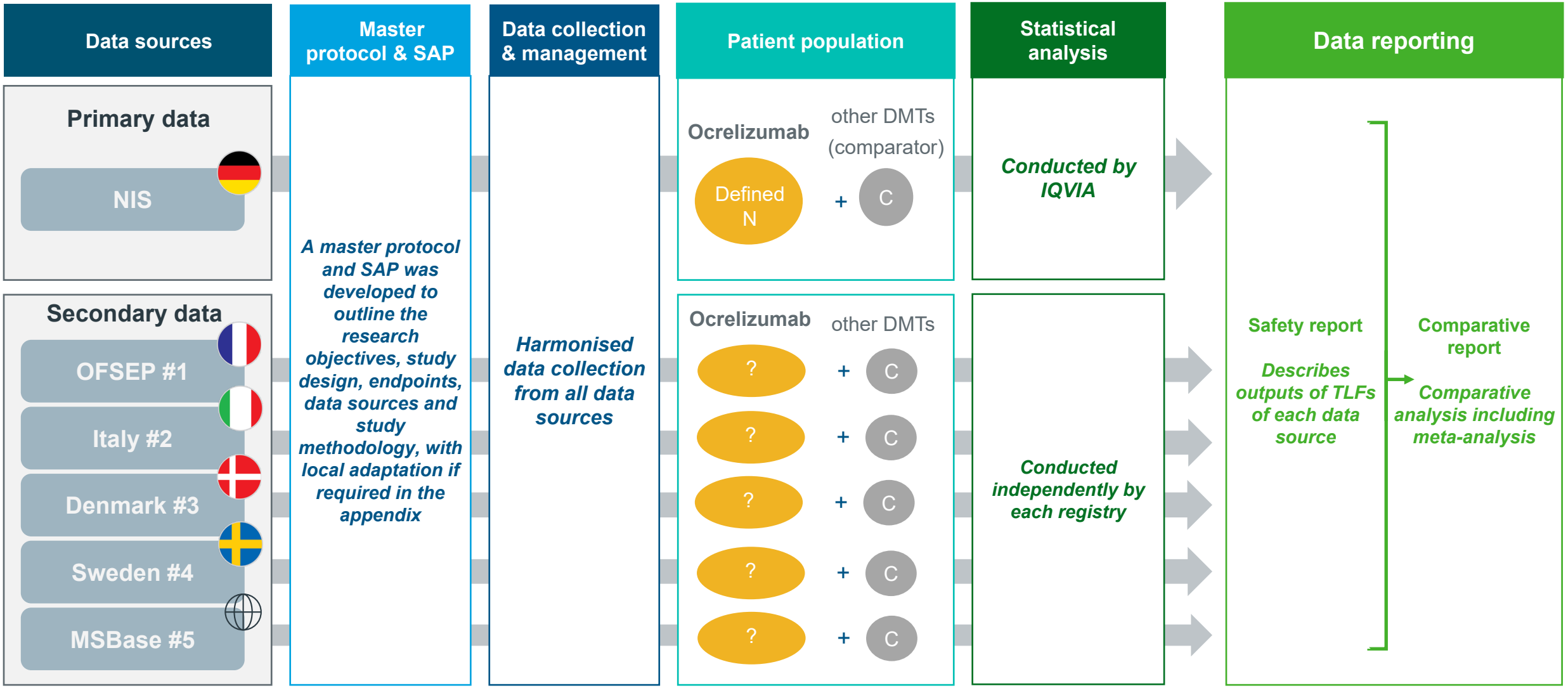
Operational considerations for accessing data, such as the availability of patient-level data and timelines for contracting, ethics and data extraction. Registries may be **challenging** to **engage** with within **required timelines**. Combining primary (NIS or site-based data collection) and secondary data and may require different analytical approaches.

The results of the feasibility assessment impacts the study design of the PASS

Adapted from EMA "Guideline for Registry-based Studies" (October 2021) and FDA "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products" (December 2023) OFSEP: Observatoire Français de la Sclérose en Plaques;

A data flow model ensures consistent data harmonisation across primary and secondary data

As patient level data could not be shared by registries, a federated analysis approach was employed



SAP: Statistical Analysis Plan; OFSEP: Observatoire Français de la Sclérose en Plaques; TLF: Tables, Listings, and Figures; DMT: Disease-modifying Therapies

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Patients were identified for the study cohort using the following inclusion and exclusion criteria

I/E criteria should be carefully considered across different data sources

I/E criteria for PASS

Inclusion criteria

- A proven diagnosis of MS
- Aged 18 years or older
- Initiated treatment with Ocrelizumab during the study observational period
- Initiated treatment with another approved DMT during the study period, i.e., patients not on DMT therapy in routine clinical practice.

Exclusion criteria

- Initiated treatment with ocrelizumab in a previous clinical trial or from a Compassionate Use program

General considerations for patient identification

Registries

- Disease registries only include **confirmed diagnosed** patients
- Patient subgroups may only be possible if included in eCRFs
  - **Early engagement with registries** is recommended to identifying potential drug subgroups and extend eCRF

EMR data

- Diagnoses are based on **ICD-10 codes**
- Clincial paramters results may be extracted in **structured and unstructured format** (phycians notes) through NLP

Claims data

- Diagnosis is based only on **ICD-10 codes**
- Clinical subgroups may be difficult to identify, e.g., patients with high progressive disease, moderate to severe scoring

References: Protocol BA39730 ocrelizumab Final v1_approved_Redacted.pdf (europa.eu)

The PASS will compare safety outcomes in an exposed cohort to an unexposed cohort

Applying a descriptive approach may be necessary in cases of limited sample size (e.g., in rare diseases)

Primary objective

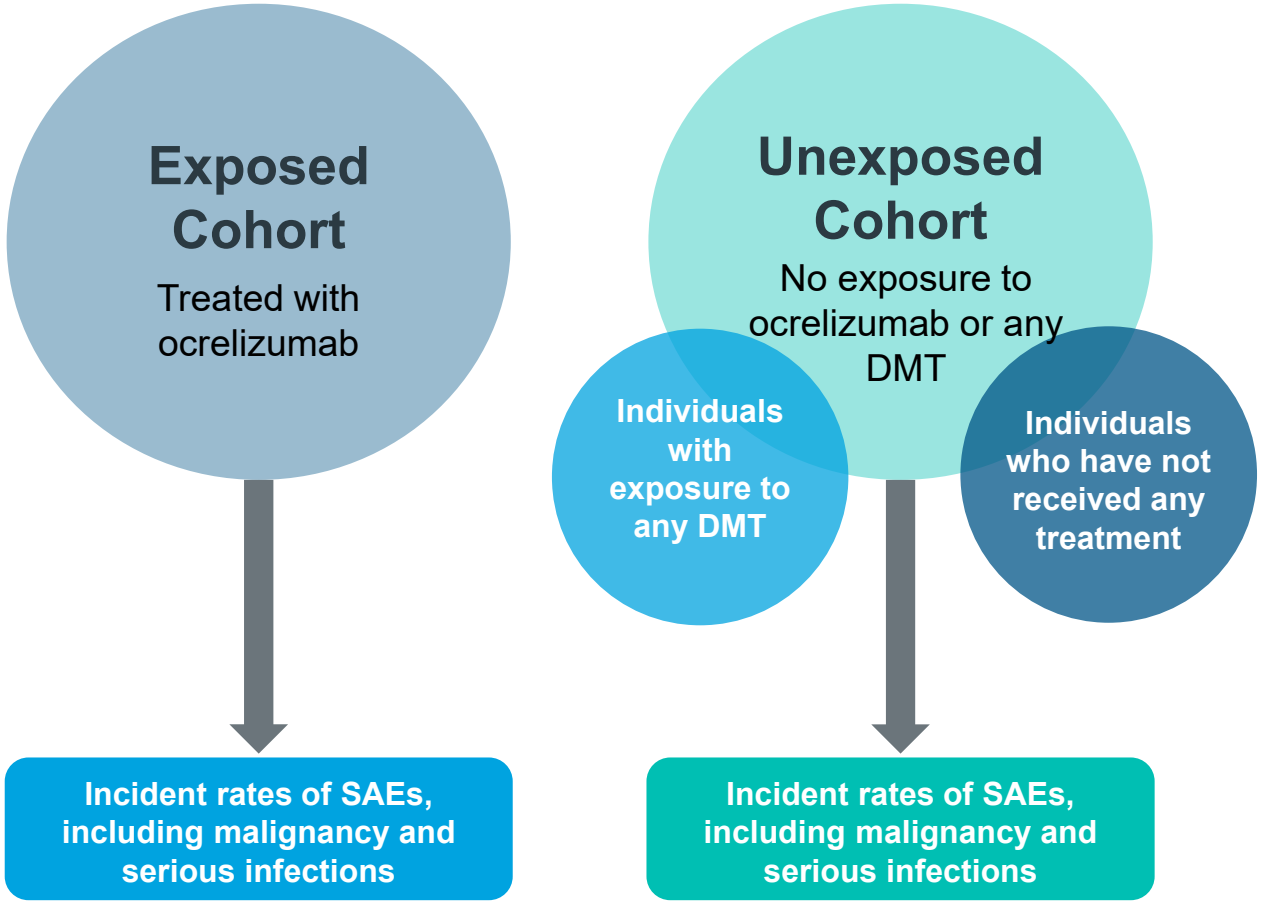
- Estimate the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment

Secondary objective

- Compare the incidence of serious safety event between ocrelizumab-exposed patients and patients exposed to other approved DMT (overall, and by individual treatment if possible), within the same data source

Exploratory objective*

- Compare the safety profile of patients exposed to ocrelizumab to the safety profile of patients not exposed to any treatment



*if sufficient data are available

References: Protocol BA39730 ocrelizumab Final v1_approved_Redacted.pdf (europa.eu)

Study design: analytical analysis is conducted within each data source

Analysis is performed based on a common core protocol and reporting template

Safety report

Safety events

- Incidence rates (involving first events only) and event rates (including all reoccurring events) per 100 patient-years with 95% confidence intervals will be calculated for all events.

Subgroup

- All rates will be reported stratified by MS subtype (overall, RMS, PPMS, other) and sex (overall, male, female).

Common reporting template used by all participating registries

Comparative report

Comparative analysis

- To compare incidence rates between treated and comparator patients, present unadjusted & adjusted HRs by using survival analysis (Cox proportional-hazard models).
- PS adjustment used to adjust for confounders
- Meta-analysis is conducted across data sources. Overall treatment effect (HR and CI) is estimated using random effects models including heterogeneity assessment
- Results are graphically displayed using forest plots.
- Different sensitivity analysis are estimated

Subgroup

- Further analyses involve subgroup analyses of absolute and relative risks by patient-level characteristics
- If patient numbers are low, descriptive analysis is conducted.

References: Protocol BA39730 ocrelizumab Final v1_approved_Redacted.pdf (europa.eu)

HR: Hazard Ratio; CI: Confidence interval, PS: Propensity score; RMS: Relapsing multiple sclerosis; PPMS: Primary Progressive Multiple Sclerosis

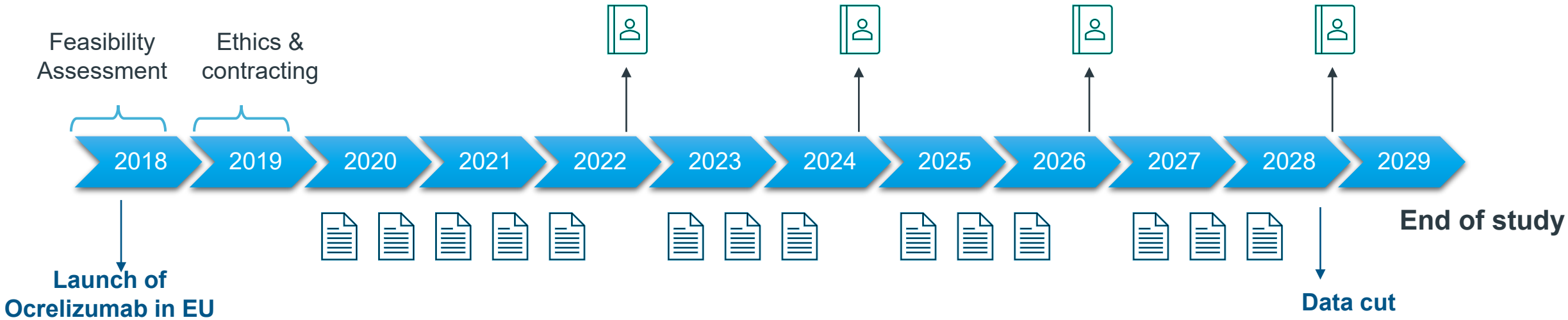
Data will be extracted biannually across the study period for semi-annual safety reports on new and cumulative safety events

Safety reports

- Aggregated data from each data source on safety events will be analysed every 6 months for 10 years until the data cut
- Focus of the safety reports is on the primary objective
- 8 safety reports have been generated so far

Comparative reports

- Every ~2 years, an interim comparative report will be developed to address the secondary objective
- A final comparative report is planned after final data cut in 2028
- 1 comparative report has been generated so far



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There are several key learnings on working with secondary data sources from our PASS

1. **Patient sample sizes**

In case of insufficient patient counts from registries, **new registries beyond the geographic scope** can be added, or **prospective data collection** in a country where asset uptake is high should be considered.

2. **Collaboration model between registries**

A **flexible approach for data integration** is necessary to support the different collaboration models with registries. **Regular meetings with registries and inclusion in report reviews** are recommended.

3. **Data quality**

On-going data monitoring and registry engagement is necessary, and **TLFs should be standardized** to allow for comparison between the different data sources

4. **Data harmonisation**

Data harmonisation (e.g., on assessments and outcomes) should be **assessed regarding validity and reliability, and feedback** to the individual registries.

5. **Report development**

Additional analyses (e.g., sensitivity analysis) to can be added incrementally into reports, depending on data availability

The ocrelizumab multi-regional, long-term PASS will improve the product's safety profile and…

Improve patient outcomes

Understanding the incidence of **malignancy** and **serious infections** will **improve patient outcomes** in MS

Reduce patients burden (& system):

RWE helps answer questions for **treatment practice with low burden to patients** due to 2ary data approach

Regulatory endorsement

Comparative interim report has been **evaluated by PRAC** & multiple **safety reports** have been **developed**

Network best practice

Targeting an EMA qualification opinion for **performing PASS** in support **of regulatory decision-making** around medicinal products


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 January 2022
EMADOC-1700519818-759902
Executive Director

Letter of Support for performing registry-based post authorisation safety studies (PASS) in Multiple Sclerosis (MS) using data of the Big MS Data Network (BMSD)

The Applicant is targeting an EMA qualification opinion of the BMSD network as well as of the individual registries for performing PASS in support of regulatory decision-making around medicinal products to treat MS. An additional aim of the EMA qualification opinion application is to establish principles regarding the addition of new registries to BMSD in the future and their possibilities of contributing to PASS.

On 04/01/2021 Karolinska Institute requested Qualification Advice for the Big MS Data network (BMSD) pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council. BMSD consisting of six participating multiple sclerosis registries, targets a context of use of performing registry-based post authorisation safety studies (PASS). A discussion meeting with the Applicant took place on 07/04/2021. On 06/05/2021, the SAWP agreed on the advice to be given to the Applicant. On 20/05/2021, the CHMP adopted the advice to be given to the Applicant.

References: https://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/29090; Minutes of the PRAC meeting on 06-09 February 2023 (europa.eu); https://www.ema.europa.eu/en/documents/other/letter-support-performing-registry-based-post-authorisation-safety-studies-pass-multiple-sclerosis-ms-using-data-big-ms-data-network-bmsd_en.pdf

Q&A

Email: Laura.girardat-rotar@iqvia.com

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