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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.

Background

BMSD was established in 2014 and consists of five national MS registries of the Czech Republic, Denmark, France, Italy, and Sweden as well as the international MSBase. The Czech Republic national MS registry ('ReMuS') collects data from all 15 MS centres in the Czech Republic. Danish MS registry ('DMSR') is a nationwide population-based register collecting information including treatment with DMT on the entire Danish MS population. Observatoire Français de la Sclérose en Plaques ('OFSEP') collects data from routine practice by participating neurologists and from all French MS expert centres. The Italian MS registry ('IMSREg') collects data by a multi-centre network of 144 MS centres in Italy. The Swedish MS registry ('SMSreg') is a quality register within the Swedish health care system and collects data from 60 neurology clinics in Sweden, and linkage to public registries is possible on a project specific basis. In contrast to the five national registries in the EU, MSBase Registry is a multi-centre, multi-national online registry based in Australia collecting data from more than 144 clinics in around 37 countries. The total number of MS patients in BMSD currently amounts to over 200.000 which represents around 10% of the global MS population.

BMSD core safety protocol

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A generic protocol—so-called 'core BMSD PASS protocol'—has been developed, in collaboration with five pharma companies working in the field of MS. This protocol aims to assess and characterise the risk of safety events in patients with MS (exposed and unexposed to approved DMTs for the treatment of MS), based on serious adverse events (SAEs) collected in the BMSD. The generic protocol lists the following four safety endpoints as primary variables: (1) malignancy, (2) non-melanoma skin cancer, (3) infection, (4) other. Information on the SAEs will be classified using MedDRA terms whenever possible by the registries.

This protocol provides a high-level concept for a future PASS, although further customization is required for a specific PASS depending on its research questions. Ultimately, the protocol to be implemented for each PASS depends on agreement between the MAH(s) and EMA/NCA. An updated generic protocol will be part of a potential future Qualification Opinion application.

The protocol lists adverse pregnancy outcomes as secondary variable, with outcomes classified using EUROCAT. Data on pregnancy in MS patients (with or without exposure to DMTs) is of particular interest and often subject to PASS. There are currently plans to develop data collections to support pregnancy studies either as part of the MS registries or as a separate pregnancy data collection; the access to pregnancy data varies across the MS registries and future pregnancy studies may not include all registries.

Aim of the EMA application

The Applicant is requesting 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 future and their possibilities of contributing to PASS.

BMSD network and PASS

The individual MS registries are distinct independent entities and provide their own governance and data management structure, and own set of quality control measures.

PASS using data from BMSD is based on secondary use of data as data for the study are collected from a registry, where clinicians not involved in the PASS have entered data in a routine fashion, either for the purpose of general research or for quality assurance in MS health care. As registries evolve, additional data items will be added if deemed of general relevance. Such items could be proposed in the context of PASS but will be implemented for all patients in the registries and use of data for PASS will remain secondary. This may limit the use of the registry for prospective studies.

The BMSD network results can be either shared as 1) aggregated data (i.e., not patient-level), for federated analysis, or as 2) individual data (i.e., patient-level data) for the analysis on pooled individual data, for example to analyse rare events. Whether to perform federated analysis where the individual registries are responsible for analysing their data locally, or for the registries to submit patient-level data to a centralized database for analysis will, to a large extent, depend on the type of project. Local regulations for some of the registries may restrict the possibilities of contributing patient-level data. The coordinating centre, for the time being, Karolinska Institutet, will be responsible for the coordination of patient-level data merge and analysis.

Based on the list of common variables to be collected, data will be cleaned and transformed into a common model (CDM) by each participating registry, to allow for merging and analysing data across the individual registries. The use of a CDM is welcomed for harmonisation purposes. According to the EMA Guideline [EMA/502388/2020], the validity of any data cleaning, extraction and transformation

processes performed centrally should be verified and monitored, especially if it involves mapping of data to a common terminology.

The Applicant explained that a PASS-specific CDM has not yet be fully completed and a standard for data quality assessment specific for PASS has not yet been specified. A quality assessment will be developed to decide whether a contributing registry has adequate quality assurance mechanisms in place to be included in the analysis. Such assessment will be based on completeness of datasets and on comparison of SAE frequencies between reporting registries; specific criteria will be developed.

Each disease registry has procedures for maintaining security and data confidentiality. All six registries are GDPR compliant. For some of the included registries no explicit consent is required, which is acknowledged.

The Applicant is advised to conduct a formal feasibility study for each of the individual registries to obtain data demonstrating they are fit for purpose. A feasibility study in context of a PASS would be very helpful to analyse the actual availability of the data elements (including relevant confounding and effect-modifying variables) as well as quality and completeness of the available data elements needed for the study. If the participating databases could deliver some overall numbers on the actual recording of patient characteristics, and particularly the recording of SAEs, this might provide assurance that several crucial elements for a PASS are captured; comedications and comorbidities are not currently collected which is considered a limitation. A validation of the recording of SAEs with hospital data (which is possible in DK and SE) would also be much welcomed. It is expected that for SAE not reported in MEDRA terms a conversion/translation to MedDRA terms is made. The results of this feasibility analysis could be put forward to support a final qualification opinion of the BMSD in the context of PASS for disease-modifying MS products that focus on these (specific) safety outcomes.

The CHMP considers that compliance to General Data Protection Regulation (GDPR) is a prerequisite for a registry to join BMSD. Reference is made to Regulation (EU) 2016/679 on the protection of natural persons regarding the processing of personal data and on the free movement of such data (https://ec.europa.eu/info/law/law-topic/data-protection/data-protection-eu_en). The Applicant should establish a concrete set of quality control indicators/definitions of common procedures for quality control which all registries joining BMSD will need to adhere to.

Summary

The EMA acknowledges the Applicant´s efforts in establishing the Big MS Data Network (BMSD) consisting of six participating MS registries to enable performing PASS studies in the context of MS and has issued this Letter of Support to encourage the further development and validation of the BMSD. Although a high-level concept for a future PASS has been provided, a common disease model and a standard for data quality assessment still need to be developed. This will be a prerequisite for the acceptance of the BMSD network as well as any future new registry to be fit for purpose in the context of a future PASS. A qualification opinion may be based on the submission of an updated generic protocol including a feasibility exercise and the introduction of a harmonized approach to quality assurance.