Big MS Data PASS FORUM

MINUTES

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On the phone: Sara Elgott, MedDay, Meritxell Sabido Espin, Merck, Cristina Pinuaga Astorga, Merck

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1. **Introduction of and update on the BigMSData project**:

BMSD visions: Large data sets, joint analyses, standards for collection and analysis, develop MS RWE BMSD includes 10% of global MS patients
BMSD started 2014
Minimal data set defined
Three demonstrator projects being run on pooled data sets
PASS and EMA: BMSD will aim for quality standard as qualified by EMA. Other MS registries can then join.
-Coordination synopsis (BMSD) describing coordination effort
-Coordination PASS
-Requested support for CC 50.000 € + OH

2. **PASS update**

Pharma were invited to present the current status of their PASS efforts.

Merck – Mavenclad (CLARION)
(Mavenclad and Lemtrada not available in France). Justify how to deal with malignancies.
Roche - Ocrevus
4 PASS (1 EMA and 3 FDA) 2 secondary data 2 preliminary data
6 data sources (BMSD + German reg). Single SAP. Meta analysis
Strong feeling of BMSD setting standards visavi regulators. Pregnancy - Germany, USA. How heterogeneity is handled (EMA)? Statisitical analysis to be shared.
Biogen – Tysabri
2016 -2024 incidence PML and SAEs. Two stage 2020 recruit and 2021-24 follow up. BMSD + UK + NTD.
Sanofi – Lemtrada
2014/15 single arm prospective, external comparison cohort. Danish and Belgian data.
New: Article 20 procedure incidence mortality and drug utilisation study.
Mortality: incidence comp to pop. cohort study, retrospective, complete mortality data, complete comorbidity data,
DUS; Prescribed, comorbidities for (prevalent) contraindications, data on monitoring.
Sanofi needs validation of single arm cohort; Proposes BMSD to use the publication format of a “cohort profile” by Int. J. Epidemiology as a key ref. Collection of key safety data is important.

Novartis – Mayzent
No PASS at the moment, but planning. Primary and secondary data? Heterogeneity? Practical issues. How to partner with BMSD? Include other data? Quality assurance? Joint protocol to use. Common QI and other aspects to be addressed by EMA and then used by pharma.
Celgene- Ozanimod
Which comparator? It, Fra, Swe. Rare events of interest. Numbers will be important. Aim to perform PASS.

Medday – Qizenday
Not there yet. See the need. Waiting phase III PP and SP - MS. Looking to file and then look for collaborations. AAN late breaking news is the aim

Reports on PASS from the registries:

MSBase
30 sites and 20.000 patients. Pregnancy data collection. Contracts to overall PASS Biogen and Roche. "Split system" CLARION, not overall MSBase PASS support
Merck and Roche (Biogen)
Denmark
Clarion, Roche, Biogen, Aubagio, Lemtrada, Pregnancy
OFSEP
SAE collected. Not much PASS. Prescription laws are special
Sanofi retrospective Lemtrada if interest
Ocrevus, Tysabri , pregnancy registry launched
Italy
13 research assistants now trained for PASS.
Biogen (01Jan 2020), CLARION (soon), Roche (process to be initiated), web system active 140 centres connected 50.000 patients. PASS to be done prospectively.
CR
15 centres within MSBase. Can participate as national registry
Swe
Clarion and Roche PASSs initiated. Biogen since before (not the Swedish BMSD team)

3. **<u>A unified analysis plan for the BMSD PASS protocol – strategic vision (Helmut B)</u>**

Core definitions need to be harmonised
Credibility of PASS protocol and PASS projects at stake – cannot risk differing results

Roche based their PASS on the BMSD Core protocol for the EMA approval.
Roche has defined their SAP using a set of definitions including, DMT exposure, event definitions and counts, time to events, time to recurring event counts, when to censor.
EMA should be positive to the use of consistent analysis plans.

Safety should be universal (as opposed to effectivity)
RW as opposed to RCTs is important

<u>Proposition:</u> BMSD and pharma take on to develop a unified analysis plan to be used by all BMSD PASS.
We will circulate the Roche ocrelizumab analysis plan (protocol). It is not product specific and could be shared.
Roche representatives agree to share.
All participating pharma representatives agree to join a work force. Helmut provisionally willing to lead.

A consensus statement on PASS an BMSD analysis plan will be published and included into the BMSD Core protocol.

4. Measures taken to optimize safety reporting by BMSD registries

BMSD registries have adjusted their data collection forms/web interfaces to optimize capture of

- Malignancies
- Non melanoma skin cancers
- Treatment-related infections, including zoster
- Other SAEs or unexpected AEs

MSBase and Italian systems based on MedDra codes directly.

5. Patient level data analysis within BMSD PASS projects

The BMSD core protocol specifies the possibility of performing analysis on pooled patient level data sets from several or all BMSD registries. So far, this is not part of any ongoing PASS.

Patient level data analyses will be important for specific questions concerning rare events or other projects that require modelling. Specific questions, specific cancers in patients with certain treatments. Matching of specific patients between countries
Governance streamlining will be required
Analysis of merged data was compared with analysis of federated data and although the latter has improved, there are still advantages in for instance modelling.

Present pharma all expressed interest in such analyses.

6. Pregnancy registries in the context of PASS

The follow-up of DMT-exposed MS pregnancies is a secondary objective in the BMSD PASS Core protocol but not yet exploited.
The BMSD registries have varying experience from collecting such data. OFSEP has focussed on pregnancies a long time and revised its collection, now a specialized registry (see below).
Roche and Merck are running separate pregnancy projects in the PASS context.

Challenges were discussed including birth outcomes.
Once a child is born it is another person and cannot be followed-up in an MS registry.
Parents may need to re-consent for their child
Choose data carefully not the exhaust patients. Pharmacovigilance is difficult to pursue. Studies to be carefully conducted.
Novartis global would be interested.
Roche has been using pregnancy registries but they can be quite limited
OFSEP/France follow children 6 years. (0, 9 months, 2 and 6 years). Include comparisons with non-MS mothers.

Kerstin Hellwig proposes TC on minimal dataset for pregnancy datasets. Beyond birth is more complicated. Involving consent on behalf of child. Proposal of minimal data set? PASS in paediatric MS? BMSD members will participate.

SUMMARY BMSD PASS:

A. There are several ongoing and planned PASS with at least some of the BMSD registries. These are typically initiated on a registry level but there will be possibilities of analysis of a joint BMSD PASS database.
B. BMSD will aim for quality standard as qualified by EMA. Other MS registries can then join.
C. A work force will be formed to deliver a unified BMSD PASS analysis plan, building on the ocrelizumab PASS analysis plan, to be published and integrated into the BMSD PASS Core protocol.
D. There is an expressed pharma interest in analysis of pooled patient level BMSD PASS data.
E. Present pharma representatives expressed an interest in BMSD pregnancy data collection in the context of PASS. Pregnancy studies may be performed in the BMSD context although there may be some issues that need to be addressed.

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7. <u>The BMSD Publication plan</u>

was briefly reviewed and updated

1.	BMSD core protocol	KI/BMSD/pharma	
2.	BMSD reference paper	KI/BMSD	April 2020
3.	Bari report (analysis focus)	DMSC/BMSD/pharma	
4.	Position paper on a BMSD PASS Analysis Plan		

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8. Other projects: BigMS opportunities outside of the PASS efforts

Research ideas invited from different parties (assessed on merit)
Governance structures of partner BMSD registries will be retained within BMSD but will be stream-lined.

A number of principally different types of projects were discussed as potentially interesting:

- Transition tables (EDSS), Disease activities
- BMSD should be the place to go and confirm specific questions
- Efficacy comparisons? Are being done individually. Complex projects but could be done in BMSD. A Bari study may address this.
- Need for standardization in RWE.

9. <u>NMO (and MOG) data</u>

There was a review of the current state.
NMO/MOG-SD data collected by MSBase, Denmark, Sweden, France, Italy, either as part of MSreg or as separate registries.
Interest in clinical care should be prime concern
HTA-required structured follow-up of newly licensed drugs: Mandatory to follow up by registries. Sweden for NMO, Spinraza and other drugs.

SUMMARY (beyond PASS):

A. There are other topics outside of PASS that may be relevant in the context of BMSD. These include comparative effectiveness of MS treatments and studies on NMO and MOG.
B. An interest in such opportunities was expressed.

10. End of meeting.

Next BMSD PASS Forum. To be expected February 2021