Regulatory Perspective on Cognitive challenges in treatment trials for epilepsy and multiple sclerosis

- Do Regulatory Guidelines address need?
- Efficacy and safety aspects
- Issues: specific claims, most appropriate tools, age…

Disclaimer

- No CoI
- The opinions expressed are personal opinions and do not necessarily reflect the official views of the Federal Institute of Drugs and Medical Devices (BfArM) or the European Medicines Agency (EMA).

EMA Guidance

- Draft Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders **(CHMP/EP/566/98 Rev.3) July 2018**
- Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis **(EMA/CHMP/771815/2011, Rev. 2) March 2015**

http://www.ema.europa.eu

Guideline for epileptic disorders

- Epilepsy constitutes /…/diverse clinical conditions /…/that entail neurobiological, cognitive, psychological and socioeconomic burden.
- Epileptic encephalopathies refer to conditions where the epileptiform activity contributes to the development of cognitive and behavioural impairment.
- The majority of paediatric epilepsies consist of age-dependent epilepsy syndromes whose manifestations are affected by ongoing brain maturation and development. Another major difference in paediatric and adult epilepsies is that some syndromes carry a grave prognosis for cognitive outcome due to the impact of epilepsy, the so-called epileptic encephalopathies.
- Early treatment with better prognosis

Guideline for epileptic disorders
Section 4 Patient selection

- The impact upon the other clinical features of the syndrome, EEG pattern or cognitive outcome for example will need to be addressed when claims are intended.
- Where an effect on the encephalopathic process itself in epileptic encephalopathies is claimed, efficacy should be shown for neurodevelopment, cognition, socialisation, EEG and not only on seizures.
- **Tools are needed.**

Guideline for epileptic disorders
Section 6.2.2 Pharmacodynamics

- The pharmacological effects on some parameters, such as cognition and/or memory and/or learning /…/ should be studied in healthy volunteers as well as in the general patient population and especially in children and elderly. Studies should include a control arm. Neuropsychological tests known to be sensitive to sedative/CNS depressive effects should be applied.

Guideline for epileptic disorders
Section 7 Safety aspects

- The design of /…/longitudinal studies will need to take into account the influence of age and underlying disease on cognition.
- Special attention should be given to the occurrence or exacerbation of CNS adverse events (e. g. those involving cognition, thought processes, memory, /…/).
- Evaluation of cognitive and neuro-motor function beyond the major disabilities requires follow-up to at least pre-school age and the use of standardized age appropriate instruments.
- Protocolised prospective disease-specific registries are recommended for long-term outcome at least up to 2-5 years.

However, no tools are recommended.

Feed-back from academia and industry required

Guideline for Multiple Sclerosis

- Targeting improvement in cognition represents a valid treament goal for new drug developments.
- Separate randomised double-blind, placebo-controlled, parallel group trials will be needed.
- Endpoints in these trials may include validated scales measuring cognitive function.
- No specific recommendation can be made about the most appropriate tool.
- Development targeting an indication based on an effect on cognition, the main efficacy data should also be accompanied by data showing improvements in function or quality of life.

Guideline for Multiple Sclerosis continued

- As cognition is a broad concept, improvement on a single item performance test will be considered as insufficient.
- It should be clear that the cognitive impairment is specifically MS related. Hence the validity of the measurements of cognitive impairment in multiple sclerosis needs to be further justified.
- Data on a functional outcome measure will be expected to be provided, in order to allow for the estimation of the clinical relevance of the symptomatic effect for the patient.

However, no tools are recommended.

Feed-back from academia and industry required

Early involvement of SAWP- What will be offered?

- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.
- **CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development

Draft qualification opinion on Multiple sclerosis clinical outcome assessment (MSCOA)

EMA/CHMP/SAWP/336445/2019

- https://www.ema.europa.eu/en/documents/scientific-guideline/draft-qualification-opinion-multiple-sclerosis-clinical-outcome-assessment-mscoa_en.pdf

1. walking (Timed 25-foot walk, T25FW)
2. hand dexterity (9 Hole peg Test, 9HPT)
3. vision (Low contrast Letter acuity, LCLA)
4. mental processing speed (Symbol Digit Modalities Test, SDMT)

Results

- Thus the connection between SDMT and ADL/function as suggested by the literature review was not reflected in the results of the Voice of Patient study and aggregated data analysis. Considering this all for the SDMT the connection between SDMT and functionality is not considered established.
- Speed of information processing is important for cognitive function but whether it covers cognitive function in MS is not made clear.
- Caveats: Learning effects, dependent on visual acuity, location of lesions

Conclusion on MSCOA

- /…/ can neither be used as a single variable or in combination with each other as primary endpoint (PEP) for measurement of disability without including functional scales as well in the PEP
- The inclusion of these tests in clinical studies as secondary endpoints in comparison to functional scales is accepted

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/SAWP/336445/2019 Correction [1]
Committee for Medicinal Products for Human Use (CHMP)

Draft qualification opinion of Multiple sclerosis clinical outcome assessment (MSCOA)

Draft agreed by Scientific Advice Working Party	14 – 17 January 2019
Adopted by CHMP for release for consultation	28 – 31 January 2019[2]
Start of public consultation	18 June 2019[3]
End of consultation (deadline for comments)	20 September 2019

Comments should be provided using this template. The completed comments form should be sent to Qualification@ema.europa.eu

Keywords	Multiple sclerosis clinical outcome assessment, Performance tests, voice of the patient study

Thank you very much for your attention

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Back-up

CHMP overall conclusion on MSCOA

While the validation work is acknowledged, the Timed 25-foot walk (T25FW), hand dexterity (9 Hole 410 peg Test, 9HPT), visual function (Low contrast Letter acuity, LCLA) and mental tests assessing processing speed (Symbol Digit Modalities Test, SDMT) can neither be used as single variable or in combination with each other as primary endpoint for measurement of disability without including functional scales as well in the primary endpoint. They could be included in a composite primary endpoint provided that a meaningful assessment of the results on EDSS or correlation with function is possible by not stopping double blind treatment and follow-up after progression on other elements of the composite and planning for an adequate number of EDSS-events (but not necessarily basing the formal power calculation on EDSS). All components should contribute to the overall effect and the overall effect should not be predominantly driven by the performance tests. It is considered that subjects, after meeting the composite event, should be followed up for all the components of the composite endpoint. The inclusion of these tests in clinical studies as secondary endpoints in comparison to functional scales is accepted.