

Cognitive Impairment in Depression: A European perspective

Prof. Dr. Karl Broich
BfArM, Germany



Relevant CHMP Guidelines

- **Guideline on clinical investigation of medicinal products in the treatment of depression**

EMA/CHMP/185423/2010 Rev. 2 (May 2013)

- **Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia**

EMA/CHMP/40072/2010 Rev. 1 (September 2012)



J Clin Psychiatry. 2014 Aug;75(8):864-76

Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review.

Keefe RS, McClintock SM, Roth RM, Doraiswamy PM, Tiger S, Madhoo M.

Conclusion:

Pharmacotherapy may have benefit in reducing cognitive impairment in MDD, with augmentation therapy being a potential approach for addressing cognitive deficits that persist after monotherapy has brought about clinical response or remission. However, given the wide variability in study design and treatment duration across studies, these findings should be interpreted cautiously. More definitive research is required before firm conclusions can be reached.



4.5.2 Efficacy on cognitive deficits

To support a separate claim for efficacy on cognitive aspects in patients with schizophrenia, specific studies should be performed. The patient population should be clearly defined in terms of a range of relevant measures of cognitive functioning. For this purpose, the cognitive test battery as proposed and defined by MATRICS is acceptable but other, comparable, test batteries may also be used provided their validity is demonstrated. A relatively younger patient population might be more appropriate for testing effect on cognition in schizophrenia, since with disease progression response to treatment of cognitive impairment may decline.

The effect of treatment on cognitive functioning should be demonstrated as the difference between baseline and endpoint on the cognitive functioning test score. Whichever tool is used, mere reduction on specific items of a larger test battery is not acceptable. In addition a functional outcome measure of clear clinical relevance to patients' functioning should be reported. Preservation or improvement of functioning as proposed for efficacy in treatment of negative symptoms would be acceptable, but the development of functional assessment instruments tailored to the assessment of treatment effects on cognitive functioning in schizophrenia is encouraged.

A study duration of at least 6 months on stable dose is recommended. Although an improvement of cognitive function might be observed after a shorter duration of treatment (e.g. 8-12 weeks), it will be necessary to demonstrate that the treatment effect is maintained over time. For this purpose, a maintenance of effect study of at least 6-12 months would suffice. Functional outcome assessed at the end of the long-term treatment period will be a particularly important secondary efficacy measure.



Schizophrenia: **Cognitive** Symptoms as Target for a Drug Treatment Claim

- Population:
 - Distinct „Cognitive Impairment“ in patients with schizophrenia
 - Generalizable to community
- Phase of the illness:
 - In stable phase without evidence of exacerbation
- Domain:
 - Spectrum of cognitive symptoms as a single target clearly preferred (MATRICS; CANTAB)
 - ~~• Not enough data to focus on specific subtypes/targets~~
- ~~• Co-Primary or~~ key secondary Endpoint:
 - **Functional outcome measure mandatory**



Functional Outcome as Endpoint

- Validated instruments for this population:
 - Yet no ideal instrument available
 - Transferable to „real world“ in the community
 - Cross-cultural adaptability
 - Proxy measures acceptable (capacity testing)
 - Sensitivity to change
- Design Issues:
 - Broad spectrum agents vs. narrow target
 - „add-on“ vs. „monotherapy“
 - Choice of control group
 - Placebo
 - Active control
 - Study duration
 - 6 months or longer
 - Maintenance of effect



Cognitive Impairment in Depression an Approvable Indication ?

Yes

- **Definition of patient population**
- **Validation of measurement tools**
 - Cognitive Measures as primary endpoint
 - Functional Measures as secondary endpoint
 - Capacity measures
 - Observer derived measures preferred
- **Mechanism of action**
 - Monotherapy approach
 - Add on-approach



