BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

MATRICS Update and Beyond: Cognition in Schizophrenia approvable?

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Disclaimer

- Personal views are presented
- Expressions cannot be regarded as official positions of EMA or BfArM
- Based on experience from applications and scientific advice procedures

Guidelines for Drug Development in Psychiatric Conditions

- Schizophrenia (CPMP/EWP/559/95 + Add.)
- Bipolar Disorder (CPMP/EWP/567/98)
- Depression (CPMP/EWP/518/97 Rev. 1)
- Panic Disorder (CHMP/EWP/4280/02)
- Generalised Anxiety Disorder (CPMP/EWP/4284/02)
- Obsessive Compulsive Disorder (CHMP/EWP/4279/02)
- Social Anxiety (CHMP/EWP/3635/03)
- Post-Traumatic Stress Disorder (PTSD) (CHMP/EWP/358650/06)
- Alzheimer‘s Disease CPMP/EWP/553/95 Rev.1)

- Insomnia (CHMP/EWP/310566/07)
- Attention Deficit Hyperactivity Disorder (ADHD) (CHMP/EWP/431734/08)
- Smoking and nicotine dependence (CHMP/EWP/369963/05)
- Alcohol dependence

http://www.ema.europa.eu

Note for Guidance-Update / Scientific Advice

- **Short-term Studies**
  - Placebo control
  - Three-arm-studies with active control and placebo
  - Duration
- **Maintenance/Long-term Studies**
  - Randomized withdrawal design (relapse prevention)
  - Parallel group extension studies
- **Endpoints**
  - Rating-scales
  - Means vs. responders
- **Specific Groups**
  - **COGNITIVE or negative symptoms**
  - **Children and adolescents**
  - Severe forms/Therapy-resistant patients
  - Elderly

Short-term Studies in Schizophrenia

- Parallel, double blind, randomized and controlled trials necessary
  - in general 6 week duration
- Choice of control
  - Placebo
  - Active comparator
  - Fixed dose studies
  - Choices must be justified by the applicant
- Three-arm or multi-arm studies preferred
  - Assay sensitivity
  - HTA-Requirements

Short-term Studies

PANSS Total Score; Model-Based Mean Change from Baseline at Endpoint; LOCF Data Set, Efficacy Sample; Key Phase III, Short-Term, Placebo-Controlled Efficacy Studies for Schizophrenia

	PANSS Total Score				
Protocol/ Treatment	N	Baseline	Change from Baseline	Treatment Difference (95% CI) versus Placebo	P-Value
31-97-201 (4-week study)					
Placebo	102	100.9	-2.9	--	--
Haloperidol 10 mg	99	99.9	-13.8	-10.8 (-17.2, -4.5)	0.0008
Aripiprazole 15 mg	99	98.8	-15.5	-12.6 (-18.9, -6.3)	0.0001
Aripiprazole 30 mg	100	99.6	-11.4	-8.5 (-14.7, -2.2)	0.0089
31-97-202 (4-week study)					
Placebo	103	94.1	-5.0	--	--
Risperidone 6 mg	95	92.6	-15.7	-10.7 (-16.6, -4.9)	0.0004
Aripiprazole 20 mg	98	93.5	-14.5	-9.6 (-15.4, -3.8)	0.0013
Aripiprazole 30 mg	96	91.6	-13.9	-8.9 (-14.8, -3.1)	0.0029
CN138-001 (6-week study)					
Placebo	107	92.6	-2.3	--	--
Aripiprazole 10 mg	103	92.9	-15.0	-12.7 (-19.0, -6.4)	0.0001
Aripiprazole 15 mg	103	92.4	-11.7	-9.4 (-15.7, -3.1)	0.0036

Assessment of Efficacy in Short-term Studies of Schizophrenia

- **Statistical Significance *and* Clinical Relevance needed**
- **Endpoints:**
  - **Primary: PANSS or BPRS**
  - **Secondary: CGI**
- **Difference between Baseline and Post-Treatment-Score**
- **30 % Improval on Standard Ratings is Considered Clinical Relevant**

Maintenance of Effect

- Short-term effects should be maintained during the episode
- Randomized withdrawal study (relapse prevention study)
  - Duration: at least 6 months
- Placebo and/or active controlled extension study
  - Parallel trial vs. active control preferred option
  - Duration: (6 to) 12 months

Schizophrenia: *COGNITIVE* or *Negative* Symptoms as Target for a Drug Treatment Claim

- **Both are considered as domains**
  - with an unmet medical need
  - which are not „pseudospecific“, but phenomenologically distinct from other symptoms
  - ***In principle approvable claims***
- **Overlap between these domains**
  - More data needed
  - Overlap would weaken possibility of separate claims
- **Do negative or cognitive results respond differently to standard antipsychotics/compounds with new mechanism of action**
  - In both domains results are disappointing

Schizophrenia: „*Cognition Claim*“

- **Population:**
  - Distinct „Cognitive Impairment“ in patients in stable phase of disease
  - *Treatment duration < 5 years*
  - Generalizable to community
- **Domain:**
  - *Spectrum of domains of cognitive symptoms as a single target clearly preferred (MATRICS; CANTAB)*
  - Not enough data to focus on specific subtypes/targets
- **Co-Primary Endpoint:**
  - *Functional outcome mandatory or not?*

Cognition and Function as Co-Primary Endpoints

- **Validated Instruments for Cognition:**
  - E.g. MATRICS, CANTAB seem to be justified
  - Transferable to „real world“ in the community („short forms)
  - Cross-cultural adaptability, generalizability to EU population
- **Validated Instruments for Function**
  - UPSA or?
  - Generalizability to Eu population
- **Design Issues:**
  - Broad spectrum agents vs. narrow target
    - „add-on“ vs. „monotherapy“
  - Choice of control group
  - Study duration
    - What is ideal? 6 months or longer
    - Maintenance of effect

Safety Issues

- Cognitive improvement at the cost of
  - More „positive“ signs or symptoms
  - Higher frequency of exacerbations
- Compounds must have shown antipsychotic properties ?
  - Avoidance of extensive polypharmacy

Other Aspects

- **Baseline therapy:**
  - OK, will go to label,
  - cognitive remediation might be acceptable if
    - Standardized, generalizable (not only within study settings)
- **Biomarkers**
  - Plausible concepts
  - Mechanism of action, specific marker
  - Proof of concept
  - Relation to disease and treatment
- **Dimensional Approaches**
  - Heterogeneity might be even larger
  - Benefit-risk-assessment even more complex

Conclusions

- **Cognition in Schizophrenia: approvable claim**
  - Cognition and Function
  - Spectrum of domains of cognition, not partial effects
  - Measures must be validated, reliable, sensitive to change
  - Clinical relevance
- Schizophrenia in general:
  - At least two short-term studies
    - Placebo and active control
    - Statistical significance and clinical relevance
  - Maintenance of effect
  - Safety requirements, risk management