BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Requirements on Medicinal Products in the Treatment of Schizophrenia

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Disclaimer

- **Personal views are presented**
- **Expressions cannot be regarded as official positions of EMEA or BfArM**
- **Based on NfG on development of medicinal products for the treatment of schizophrenia**

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)

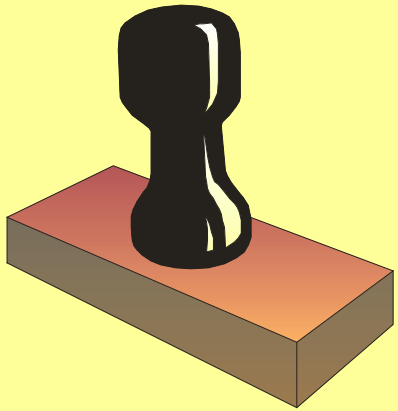
- Insomnia (CHMP/EWP/310566/07)
- Attention Deficit Hyperactivity Disorder (ADHD) (CHMP/EWP/431734/08)
- Smoking and nicotine dependence (CHMP/EWP/369963/05)
- Alcohol dependence

http://www.emea.europa.eu

„Approval of a Medicinal Product“

- ***Efficacious*** **under experimental trial conditions with effects, which can be regarded as clinically meaningful**
- ***Safe*** **(acceptable side effect profile, without major risks)**

- **Approval, if overall *benefit-risk is positive !***



„efficacy“ vs. „effectiveness“

- **„Efficacy“**
  - Pure efficacy of a therapeutic intervention in a controlled setting
    - gold standard: randomised, controlled, double-blind clinical trial with high internal but low external validity
- **„Effectiveness“**
  - Efficacy of a therapeutic intervention in real world conditions of everyday practice in the community with low internal but higher external validity
    - Many,many confounders
- **What can we learn from the distinct approaches?**
- **However, what regulators must know for approval?**

Effectiveness-Studies in Schizophrenia

- CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness):
  - Schizophrenia
  - Alzheimer‘s disease
- STAR*D (Sequenced Treatment Alternatives to Relieve Depression)
- STEP-BD (Systematic Enhancement Program for Bipolar Disorder)

- CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study)
- EuroSC (European Schizophrenia Cohort)
- SOHO (Schizophrenia Outpatient Health Outcomes)

Eur Arch Psychiatry Clin Neurosci (2008) 258:257–270
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ORIGINAL ARTICLE

Hans-Jürgen Möller

Do effectiveness ("real world") studies on antipsychotics tell us the real truth?

Approval decision of regulatory bodies will be based on efficacy and safety established by RCT!

Note for Guidance / 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)
- **Endpoints**
  - Rating-scales
  - Means vs. responders
- **Specific Groups**
  - Severe forms
  - Elderly
  - Children and adolescents
  - Therapy-resistant patients
  - Negative or cognitive symptoms

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**

Study Designs in Schizophrenia

- **Three adequate and well controlled designs possible:**
  - **Placebo control** **Superiority**
  - **Dose comparison** **Superiority**
  - **Active control** **Superiority or Equivalence/Non-Inferiority**
- **Non-Inferiority Design tested in most cases**
  - **New drug is not inferior by more than some predefined amount** ➔
  - **Non-Inferiority Margin**
    - **To define this margin „assay sensitivity“ has to be known**

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

Short-term Studies

Table 10: Treatment assignments in the four short-term phase III studies.

	Treatment Group						
		ER OROS Paliperidone (mg/day)					Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	10mg/day
Key Efficacy Studies in Subjects at Least 18 years of age with Schizophrenia							
R076477-SCH-303	X		X	X	X		X
R076477-SCH-304	X		X		X		X
R076477-SCH-305	X	X		X		X	X
Safety and Tolerability Study in Elderly Subjects with Schizophrenia							
R076477-SCH-302	X	3 mg to 12 mg/day					Not Included

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**

Responder Analysis: 30% improvement in PANSS-Scores

In the responder analyses significantly more responders were observed in all paliperidone groups (56%, 51% and 61% in the 6 mg, 9 mg and 12 mg groups, respectively, $p<0.001$ for all doses) compared to the placebo group (30%).

In the responder analyses significantly more responders were observed in both paliperidone groups (50%, $p=0.025$ and 51.4%, $p=0.012$ in the 6 mg and 12 mg groups, respectively) compared to the placebo group (34.3%).

In the responder analyses significantly more responders were observed in all paliperidone groups (40%, 46% and 53% in the 3 mg, 9 mg and 15 mg groups, respectively, $p<=0.001$ for all doses) compared to the placebo group (18%).

Maintenance of Effect

- Short-term effects should be maintained during the episode
- Randomized withdrawal study (relapse prevention study) is the preferred design
- Duration: at least 6 months
- Placebo-controlled extension study possible alternative, but not preferred

Randomized Withdrawal Study

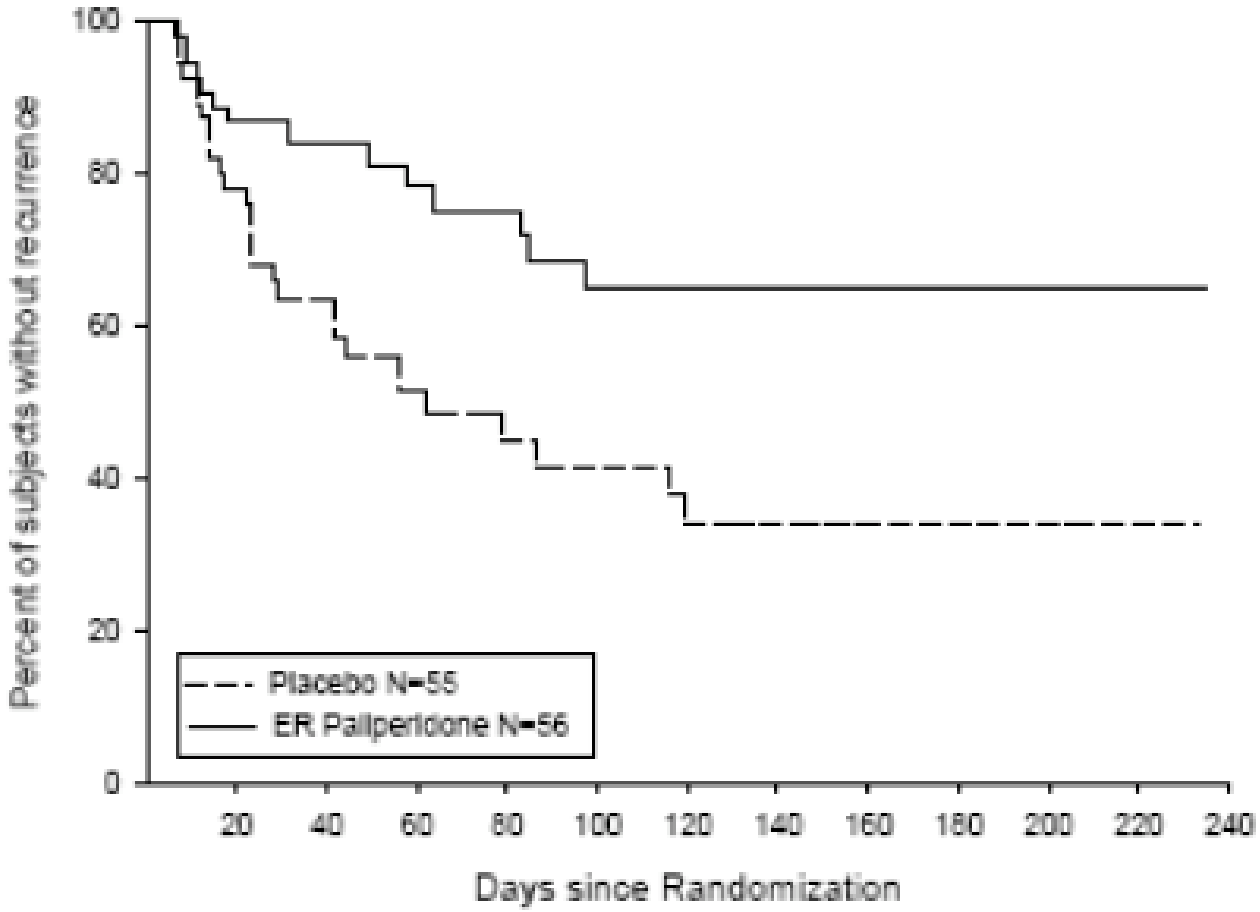

Figure 12: Time to recurrence in Study SCH-301. ITT population, interim analysis.

Specific Age Groups

- **Elderly**
  - Different pharmacokinetics/pharmacodynamics
  - High rate of comorbidity
  - Safety profile
- **Children and Adolescents**
  - Efficacy
    - Short-term and maintenance ?
    - Different assessment tools ?
  - Safety Profile
    - Cognition and learning
    - Endocrine, sexual and growth functions
- **Therapy Resistant Patients**

Schizophrenia: *Negative* or *Cognitive* Symptoms as Targets 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**
- Overlap between these domains
  - **More data needed**
  - **Overlap would weaken possibility of separate claims**
- Do negative or cognitive results respond differently to standard antipsychotics ?
  - **In both domains results are disappointing**

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

- Population:
  - **„prominent negative symptoms“**
- Phase of the illness:
  - **In stable residuum**
- Domain:
  - **Spectrum of negative symptoms as a single target clearly preferred**
  - **Not enough data to focus on specific subtypes/targets**
- Co-Primary Endpoint:
  - **Functional outcome as secondary endpoint**

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

- Population:
  - **Distinct „Cognitive Impairment“ in patients with schizophrenia should be further established**
  - **Generalizable to community**
- Phase of the illness:
  - **In stable residuum**
- Domain:
  - **Spectrum 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**

Functional Outcome as Co-Primary Endpoint

- Validated instruments for this population:
  - **Yet no ideal instrument available**
  - **Transferable to „real world“ in the community**
  - **Cross-cultural adaptability**
- 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**

Conclusions

- **At least two positive short-term studies**
  - Placebo and active control
  - Statistical significance and clinical relevance
- **One study: Maintenance of effect**
  - Relapse prevention (randomized withdrawal design)
- **Ongoing discussions**
  - Special populations
    - Age related issues: children and adolescents
    - Cognition, negative symptoms
  - Safety requirements, risk management
  - Diagnostic criteria of DSM-V / ICD-11