# Negative symptoms in schizophrenia: a target for drug development. The European perspective.

Cristina Sampaio MD, PhD
Professor Clinical Pharmacology and Therapeutics
University of Lisbon, Portugal
Member of CHMP and SAWP, EMEA

# Summary

- Negative symptoms in schizophrenia.
  - Are these acceptable targets for drug development?
  - If, yes in which conditions?
    - The concepts
    - The populations
    - The trial design
  - Comment to the FDA discussion paper

    Schizophrenia Bull 2005, doc 10.1093

# Negative symptoms 1

- Schizophrenia Note of Guidance
  - CPMP/EWP/559/95, enforced 08/98
    - Negative symproms must be recognized as a specific feature of the disease and not just secondary to the psycosis, ADR, depression, understimulation.

Also FDA

    - Claims can only be made if negative symptoms are clear defined and if the effect can be deonstrated as a direct effect.

Also FDA

    - It is not sufficient to record a favourable change in a negative symptoms scale.

# Negative symptoms 2

- Schizophrenia Note of Guidance
  - CPMP/EWP/559/95, enforced 08/98
    - Sophisticated statistical methods like path analysis and regression models cannot be more than supportive data.
  - Proposed trial design
    - 3 arm, parallel, placebo and active control
    - 8 weeks or longer
    - Not in the acute phase if the intention is a mention in the indication.

**FDA 2 arm wo PL or add-on.**

**FDA suggest 6m.**

**FDA discards acute.**

# Negative symptoms 3

- Schizophrenia Note of Guidance
  - CPMP/EWP/559/95, enforced 08/98
    - Population
      - Predominant and persistent negative symptoms
      - Stable condition of the schizophrenic illness>6m with predominate neg symptoms.
      - Flat of affect and poverty of speech represent the core negative symptoms, though the extent may differ between pts.
      - Major depression should be excluded;low depression scores are preferable.
      - Accounting for effects on EPS

**FDA admits dif. Domains of neg symp.**

# Negative symptoms 4

- Schizophrenia Note of Guidance
  - CPMP/EWP/559/95, enforced 08/98
    - Evaluation
    - Discard BPRS
    - PANSS and SANSS recognized as having validity
    - Scales for depression and EPS should also be incorporated.

**FDA may want a global functional mesurment as co-primary.**

# Conclusions

- Negative symptoms were clearly recognized as a target by CHMP.
  - Probably to early
- The guideline statements are still correct in many aspects but the discussions about trial design need update.