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The design of a double-blinded, active-controlled, randomized study in treatment resistant schizophrenia

Authors: Walling D[1], Forray C[2], Hertel P[3], Löf E[3], Kane J[4]

[1]-CNS Network, LLC, Long Beach, California, USA
[2]Lundbeck Pharmaceuticals LLC, New Jersey, USA
[3]H Lundbeck A/S, Valby, Denmark
[4] Hofstra Northwell School of Medicine, The Zucker Hillside Hospital, Hempsead, New York, USA

The methodological question being asked

A confirmatory study was designed in alignment with available guidelines to test the efficacy and safety of a potential new medication for treatment-resistant schizophrenia (TRS) [1,2].

Introduction (aims)

It is estimated that more than 21 million people worldwide are affected by schizophrenia, and that up to a third of these have treatment resistance. TRS is defined as a failure to respond to two trials of different antipsychotic agents of adequate dose, duration and adherence. TRS has severe humanistic, clinical and economic impact on patients, family, caregivers, and society. At present, clozapine is the only approved treatment for TRS but is associated with serious safety issues. There is a need for a new efficacious treatment with a better safety profile based upon clinical trials that demonstrate these effects.

Guidelines on TRS study design are available from the consensus working group TRRIP [1] and the EMA [2]. The EMA guideline states that study design and choice of endpoints in TRS are essentially the same as for other schizophrenia trials. Key differences are the definition of the patient population and the choice of comparator. It is important to adequately assess that the included patients have TRS and that the lack of response is not a consequence of poor medication adherence. For the choice of comparator, there are two possibilities: demonstration of non-inferiority to clozapine or superiority to an active comparator, with which treatment failure has been documented.

The current study design aimed at operationalizing these key points.

Methods

The suggested study design was based on discussions with the FDA and in line with the TRRIP and EMA guidelines.

Results

The study adheres to the definition of TRS, as patients were identified by both a retrospective and prospective trial of antipsychotic treatment. Retrospectively, the patients should have shown lack of response in the level of psychotic symptoms despite at least one documented treatment trial with an adequate dose of an antipsychotic agent prescribed for ≥ 6 weeks during 2 years prior to screening. In the prospective confirmation of TRS (Phase A) patients were treated for 6 weeks with risperidone (6 mg/day), or if currently under treatment with risperidone, with olanzapine (15 mg/day). Both are second-generation antipsychotics with well-established efficacy and safety

profiles. Treatment adherence in the prospective phase and the rest of the study was documented by pill count and by measuring the plasma level of medications. Patients who adhered to the prospective treatment and did not show treatment response were defined as having TRS, and were randomized to either stay on risperidone/olanzapine or switch to the investigational product for 10 weeks (Phase B). The primary endpoint was symptoms of schizophrenia as change from baseline of period B to week 10 of period B in PANSS total score.

The aim was to show superiority of the investigational product over the control group, which was continuation of the assigned treatment.

Conclusions

Presented is a study design for assessing monotherapy of TRS in alignment with available regulatory and clinical study guidelines.

Disclosure (if relevant)

Elin Löf and Peter Hertel are employees of H. Lundbeck A/S. Carlos Forray is an employee of Lundbeck Pharmaceuticals LLC.

References

1 Howes, OD, McCutcheon, R, Agid, O, et al. 2017. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guideline on Diagnosis and Terminology. Am J Psychiatry 174, 216–229.

2 EMA. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia. CHMP/40072/2010 Rev. 1