ORIGINAL RESEARCH

Key Words: asenapine, clinical trial, study design, negative symptoms, schizophrenia

Asenapine in the Treatment of Negative Symptoms of Schizophrenia: Clinical Trial Design and Rationale

By Larry Alphs, MD, PhD, John Panagides, PhD, and Scott Lancaster, MS

ABSTRACT ~ Although the positive symptoms of schizophrenia are more likely than the negative symptoms to result in a patient’s hospitalization, positive symptoms tend to respond more completely to antipsychotic drugs. When positive symptoms are controlled, residual negative symptoms may remain. If these negative symptoms persist, they can have a considerable impact on a patient’s ability to function in society. Current therapies have only a limited effect on negative symptoms. Consequently, broad-spectrum agents that effectively treat both positive and negative symptoms are needed. One obstacle to the regulatory approval of an agent for treating negative symptoms is the difficulty of designing a trial to demonstrate efficacy for these symptoms. Agreeing on a definition of negative symptoms, establishing patient inclusion criteria, and determining how to account for confounding factors represent only a few of the challenges to study design. Here these challenges can be met is illustrated in the design of a series of clinical trials to assess the efficacy of asenapine, a psychopharmacologic agent being developed for the treatment of schizophrenia and, in particular, the treatment of negative symptoms associated with schizophrenia. These trials, the protocols for which are described in this paper, will not only determine the efficacy of asenapine but will add to our knowledge of patients with predominant, persistent negative symptoms, an understudied and inadequately treated patient population. Psychopharmacology Bulletin. 2007;40(2):41-53.

INTRODUCTION

Schizophrenia encompasses various symptoms, including both overt positive symptoms and the less obtrusive, but often more psychosocially devastating, negative symptoms. Negative symptoms are a loss of normal function, with patients displaying decreased emotional expressivity and perception, reduced fluency and productivity of thought and speech, reduced desire for social involvement and social interaction, and a loss or lack of goal-directed behavior, all of which have consequences for a patient’s ability to function in society.
Negative symptoms can occur in schizophrenia regardless of the stage of illness. Indeed, they may be an early sign of schizophrenia, with social withdrawal and decreased motivation preceding a first psychotic episode. Negative and positive symptoms can coexist in the same patient, but it is the positive symptoms that are more likely to result in hospitalization. When positive symptoms are controlled with antipsychotic medication, persistent negative symptoms may predominate as a key area of dysfunction.

Currently available antipsychotics, both conventional and atypical agents, are effective for treating the positive symptoms of schizophrenia. Conventional antipsychotics, however, appear to have an insufficient effect on negative symptoms, and although some atypical agents may have a modest therapeutic effect on these symptoms, it remains unclear whether the effect is direct or indirect. Thus, despite the therapeutic effects of our best treatments, treatment of negative symptoms remains a significant unmet need.

In this report, we discuss some of the challenges encountered when designing clinical trials to assess a drug's efficacy for negative symptoms and describe how these challenges have been met in clinical trials of asenapine, a psychopharmacologic agent in development for the treatment of schizophrenia and bipolar disorder. These asenapine studies, referred to collectively as the Aphrodite trials, consist of two 26-week, multicenter, double-blind, flexible-dose trials that compare asenapine with olanzapine in stable patients with predominant, persistent negative symptoms of schizophrenia. Each 26-week study is followed by a 26-week blinded extension trial, for a total study duration of 52 weeks.