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Long-term effects of asenapine or olanzapine in patients with persistent negative symptoms of schizophrenia: A pooled analysis

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ABSTRACT

Background: A Phase 2 efficacy study suggested that asenapine (ASE) was superior to risperidone in decreasing negative symptoms in schizophrenia at 6 weeks, prompting design of two negative symptom studies. Two 26-week core studies with 26-week extensions compared asenapine (ASE: 5–10 mg twice-daily] and olanzapine (OLA: 5–20 mg once-daily) as monotherapies in reducing persistent negative symptoms (PNS). While neither study met the primary endpoint of superiority of ASE over OLA, ASE was statistically superior to OLA in one extension study. This prompted a pooled analysis of the treatment effects of both drugs.

Methods: Data were pooled from two 26-week core studies and extensions. Efficacy endpoints: change in Negative Symptom Assessment scale-16 (NSA-16) total score at Week 26 (prespecified primary endpoint) and Week 52. Additional measures: change in Positive and Negative Syndrome Scale (PANSS)-total, Marder factors, negative subscale scores, Clinical Global Impression Severity of Illness score (CGI-S) assessments, NSA-16 factor domains, NSA global score, and individual items.

Results: Pooled data from the extension studies ($n = 502$) showed no differences between ASE and OLA at Week 26. At Week 52, ASE showed superiority over OLA in NSA-16 total score, NSA global, PANSS Marder negative and PANSS negative subscales, some NSA-16 items, and four of five factor domains. In addition, pooled data for patients who entered the core trials ($n = 949$) were analyzed over 52 weeks (whether or not patients entered the extension). No significant differences between groups were observed in change in NSA-16 total score at 26-weeks. At Week 52, ASE was significantly superior over OLA in this measure, NSA global score and PANSS Marder negative factor. There were more early dropouts due to AEs, including worsening of the disease, in the ASE group.

Conclusion: In this pooled analysis, ASE and OLA did not differ significantly over 26 weeks, but indicated a signal of superiority for ASE with continued treatment up to 52 weeks.

1. Introduction

Despite the availability of a number of effective antipsychotic drugs for the treatment of patients with schizophrenia, not all clinically relevant symptom domains are controlled to the same degree in a majority of patients with any of the available drugs. While in acutely ill patients antipsychotics tend to improve positive symptoms and some general symptoms associated with the acute state within a few days to a few weeks to an acceptable level, in a sizeable group of patients the clinical symptoms of cognitive impairment or negative symptoms are generally less responsive to drug treatment. In the longer term of the disease course, these symptoms have been increasingly recognized as highly relevant for patient outcome and individual prognosis. Negative symptoms of schizophrenia such as avolition, anhedonia, affective flattening, and poverty of speech are associated with poor social functioning leading to long-term morbidity, poor functional outcome, impaired relationships, and poor prognostic outcomes (Ho et al., 1998; Milev et al., 2005; Siegel et al., 2006). A population-based birth cohort in Finland demonstrated that 41% of first-episode subjects had negative symptoms and 39% had negative symptoms at 10-year follow-up (Makinen et al., 2010).

Negative symptoms have been conceptualized in various ways, e.g., as primary or secondary negative symptoms (for review see Buchanan, 2007). Accordingly, primary and enduring negative symptoms or deficit symptoms are present during and between episodes of positive symptom exacerbation and are observable regardless of medication status. From a clinical perspective, negative symptoms persisting over a longer period of time appear particularly relevant as target symptoms for treatment intervention. The chronicity and the persistence of negative symptoms appear relevant factors for detrimental effects on functional outcome and associated disease burden (Provencher and Mueser, 1997; Norman et al., 2000). The concept of persistent negative symptoms (PNS), usually defined as negative symptoms present for ≥6 months, not associated with the onset or

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recovery from an acute exacerbation of the illness, and are comprised of primary or secondary negative symptoms unresponsive to treatment (Buchanan, 2007). Secondary negative symptoms, on the other hand, may be a consequence of depression or an extrapyramidal symptoms (EPS) side-effect of antipsychotic medication.

Despite the clinical importance of PNS in schizophrenia, very few pharmacotherapies have specifically targeted these symptoms in dedicated controlled studies. From a drug development perspective, currently no antipsychotic treatment has gained FDA approval for PNS. However, in a continued dialogue with drug developers and academic clinical researchers, the FDA recently clarified their position on negative symptoms and/or cognitive impairment of schizophrenia as clinical targets for drug development (Laughren and Levin, 2006, 2011). While, in principle, they acknowledge the medical need for treatments in these areas, they also point out the requirement to study treatment effects in appropriate designs and clinical settings in order to be able to demonstrate a more specific effect on these symptom domains.

Asenapine (ASE) is an antipsychotic agent indicated in the United States and Canada for the treatment of adults with schizophrenia and as monotherapy or adjunctive therapy with lithium or valproate in the treatment of manic or mixed episodes associated with bipolar-1 disorder (Saphris, 2013). The multi-affinity pharmacologic profile of ASE is evident from its potent binding to a large number of receptor subtypes in serotonergic, adrenergic, and dopaminergic systems (Shahid et al., 2009) and distinguishes it from other second generation antipsychotics. During the development program for asenapine, a 6-week, randomized, placebo-controlled study for ASE that used risperidone as an active control showed that both drugs were superior to placebo in treating the positive symptoms of schizophrenia, but only ASE demonstrated superiority over placebo in treating negative symptoms (Potkin et al., 2007). Treatment of PNS may require prolonged treatment and given the short-term duration of the study and acute treatment setting, there was a need to further assess the effects of ASE treatment on negative symptoms in a dedicated treatment setting of patients stabilized for their acute symptom and still experiencing persistent negative symptoms requiring targeted treatment.

Therefore, a clinical program was designed to test for superiority of ASE compared with olanzapine (OLA) as monotherapies in reducing negative symptoms in a population of patients with persistent PNS. Two 26-week randomized, double-blind core studies were conducted, one in the Eastern Hemisphere (EH) and one in the Western Hemisphere (WH), with the Negative Symptom Assessment scale-16 (NSA-16) as the prespecified primary outcome measure using the Mixed-Effect Model Repeated Measure (MMRM) model as primary analysis. Each study had an optional 26-week blinded extension. Results of these studies have been published (Buchanan et al., 2012). Briefly, at 26 weeks (core studies) both ASE and OLA substantially reduced PNS with no significant differences between treatment groups in the primary prespecified outcome measure (change in NSA-16 total score). However, at 52 weeks in one of the extension studies (WH) ASE showed significant superiority over OLA in reducing PNS in the primary outcome measure.

Based on results from the WH extension study, a pooled analysis was undertaken to explore potential superiority of ASE over OLA in reducing PNS from this program. For the purpose of this analysis, the two core studies and their extensions were pooled and the 1-year data were assessed for treatment outcomes using a mixed model for repeated measures (MMRM) analysis as in the original studies.

2. Methods

2.1. Primary studies

The study design and patient population have been described elsewhere (Buchanan et al., 2012). Briefly, the four phase 3 double-blind studies that compared flexible-dose ASE (5 or 10 mg twice-daily) with flexible-dose OLA (5–20 mg once-daily) included two 26-week randomized core studies and corresponding 26-week extensions conducted in 15 EH countries and 5 WH countries between May 2005 and May 2009 (EH: clinical trials registry identifiers NCT00212836 and NCT00265343, respectively; WH: clinical trials registry identifiers NCT00145496 and NCT00174265, respectively). Subjects completing either of the core studies and considered to potentially benefit from continued treatment were eligible to participate in the extension studies with the blinded core study treatment regimen (Buchanan et al., 2012).

Eligible subjects for the core studies were those aged 18 years and older with a current diagnosis of schizophrenia, Positive and Negative Syndrome Scale (PANSS) negative symptom subscale score $\geq$20 at screening and baseline, and scores $\geq$4 (moderate) on three or more of the seven PANSS items of the negative symptom factor (blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, lack of spontaneity, motor retardation, active social avoidance). Subjects were excluded if they had clinically significant EPS or depression to exclude secondary negative symptoms or effects of psychosis as measured by the following scores: Extrapyramidal Symptom Rating Scale Abbreviated global Parkinson item score of 3 or greater, a Calgary Depression Scale for Schizophrenia total score of 9 or greater, or a rating of 4 or greater on two or more PANSS positive symptom subscale items. Patients with a history of nonresponse or intolerance to OLA were also excluded from participation in the studies.

In addition, subjects had to be clinically stable for 5 months before screening on any type of antipsychotic drug treatment such as first generation antipsychotics, second generation antipsychotics or depot formulations, or combinations thereof. After inclusion in the study, patients were required to demonstrate continued stability for 1 prospective month on the same treatment regimen without substantial changes, defined as no screening to baseline change of $\geq$20% in Clinical Global Impression Severity of Illness (CGI-S) score and screening to baseline changes in PANSS total score and PANSS Marder factor negative symptom score. After a total of $\geq$6 months of retrospective and prospective stabilization on any drug treatment, patients were randomized to receive ASE or OLA. This double-blind, double-dummy study medication was given on Day 1 in addition to the previous drug regimen. Previous treatments were subsequently tapered off at the discretion of clinicians within 4 weeks. After this period, study medication was continued as a monotherapy in all patients up to 26 weeks, followed by an option for a 26-week extension of blinded medication.

The primary efficacy measure used in each study was the NSA-16 total score. The prespecified efficacy measure was the change in NSA-16 score at Week 26. The NSA-16 instrument, which has a high inter-rater and test–retest reliability across languages and cultures, examines the presence, severity, and range of negative symptoms associated with schizophrenia (Alphs et al., 1989; Axelrod et al., 1993; Daniel et al., 2011). In addition to NSA-16 total score, NSA global scores, PANSS total and negative subscale scores, the PANSS Marder factor scores (positive, negative, and anxiety/depression), and the CGI-S scores were utilized as secondary efficacy measures. Efficacy assessments were conducted at screening, baseline, and Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 26 in the core and every 4–6 weeks in the extension studies.

2.2. Pooled analyses

As the clinical characteristics of subjects were comparable within treatment groups in EH and WH studies, and the designs were equivalent, the 52 weeks data comprising core and extension populations from EH and WH studies were pooled for the respective treatment groups (Fig. 1). Treatment outcomes were assessed using MMRM analysis in the intent to treat (ITT) populations (randomized