European Neuropsychopharmacology (2013) 23, 1043–1050

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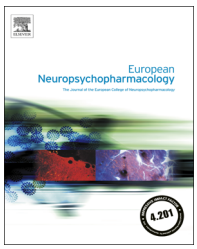

Does early improvement predict response to the fast-dissociating D_2 receptor antagonist JNJ-37822681 in patients with acute schizophrenia? ☆, ☆ ☆

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Received 14 June 2012; received in revised form 24 August 2012; accepted 25 August 2012

KEYWORDS
Antipsychotic agents;
Dopamine antagonist;
JNJ-37822681;
Olanzapine;
Schizophrenia

Abstract
Early predictability of sustained response to atypical antipsychotics in patients with schizophrenia has important implications for clinical decision making. In order to investigate whether early onset of efficacy correlates with week-6 response for the selective fast-dissociating D_2 receptor antagonist JNJ-37822681, we analysed data from a 12-week placebo- and active-controlled (olanzapine) study designed to evaluate efficacy and safety of JNJ-37822681. Factors, including baseline Positive and Negative Syndrome Scale (PANSS) total score, waist circumference, weight, body mass index group, number of previous hospitalisations, age at diagnosis, race, sex and age at study entry, and relative (%) change from baseline on day 3 (early improvement) in PANSS total score, were analysed using logistic regression models and receiver operator characteristic (ROC) curve analysis, to predict the week-6 efficacy response ($\geq$30% improvement in PANSS total score). Results showed that week-6 response with JNJ-37822681 30 mg bid treatment could be reliably predicted by improvement in PANSS total score on day 3, the number of previous hospitalisations, and race (80% accuracy [ROC area under curve]). Early improvement (day 3) in PANSS score had the highest predictive value as a single factor across all JNJ-37822681 doses. At a specificity of 70%, sensitivity for predicting week-6

☆ *Trial registration:* The study is registered at clinical trials. gov as NCT00728195.

☆ ☆ *Previous publications and presentations*: The primary results from this study are submitted elsewhere. Data in the manuscript were previously presented as a poster at the 66th Annual Convention and Scientific Program of the Society of Biological Psychiatry (SOBP), held in San Francisco, CA, USA from 12 to 14 May 2011; the 51st Annual Scientific Meeting New Clinical Drug Evaluation Unit (NCDEU), held in Boca Raton, FL, USA from 13 to 16 June 2011; and the 24th European College of Neuropsychopharmacology (ECNP) Congress, held in Paris, France, from 3 to 7 September 2011.

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0924-977X/$ - see front matter
http://dx.doi.org/10.1016/j.euroneuro.2012.08.017

response was: 0.60, 0.64, and 0.74 in the 10-, 20-, and 30 mg bid JNJ-37822681 groups, respectively; 0.40 in olanzapine group. Early improvement in PANSS may be a simple and reliable way to predict sustained response with JNJ-37822681 in patients with acute schizophrenia.

1. Introduction

An increasing body of evidence suggests that antipsychotic effects are observable early in the treatment of acute schizophrenia, with the majority of improvement occurring relatively early, within 2–4 weeks of starting treatment (Agid et al., 2006; Correll et al., 2003; Kinon et al., 2010a, 2010b). Furthermore, the "delayed-onset hypothesis of antipsychotic action", which suggested that 6–8 weeks are required to determine a therapy's effectiveness in patients with schizophrenia has been largely rejected (Agid et al., 2003, 2006; Ascher-Svanum et al., 2008; Levine and Leucht, 2010; Kinon et al., 2010b). Meta-analyses and post hoc analyses of data from randomised controlled trials in the treatment of schizophrenia have demonstrated that early nonresponse (at 1 or 2 weeks) to treatment with antipsychotic agents appears to be a robust predictor of subsequent nonresponse (Agid et al., 2003; Ascher-Svanum et al., 2008; Correll et al., 2003; Leucht et al., 2005, 2007; Kinon et al., 2008). Likewise, a recent study in patients with acute schizophrenia indicated that an early response ($\geq$30% improvement from baseline in PANSS total score at week 4) to antipsychotic medication may serve as an early clinical marker that clinicians can use to balance the benefit and risk of treatment (Ascher-Svanum et al., 2011).

Further, some studies also suggest that early response potentially predicts sustained response in schizophrenia (Kinon et al., 2010a, 2010b; Suzuki et al., 2011). Results from an analysis of pooled data from 5 double-blind, randomised trials with second-generation antipsychotics identified specific thresholds of response at early time points (weeks 1–4) for predicting subsequent response ($\geq$30% improvement from baseline in PANSS total score) or nonresponse at week 8 of treatment (Chen et al., 2009). Moreover, early nonresponse to treatment with antipsychotic agents may predict failure to achieve remission: a post hoc analysis of data from a randomised trial in patients with chronic schizophrenia treated with both typical and atypical antipsychotics showed that those who do not experience early response ($\geq$20% improvement in PANSS total score from baseline at week 2 of treatment) had significantly poorer subsequent treatment outcomes when the same antipsychotic medication was continued for an additional 6 weeks (Ascher-Svanum et al., 2008). Further studies involving larger patient groups, frequent early symptom ratings and treatment durations longer than 4 weeks are needed to better determine the predictive value of early response for ultimate treatment response (Correll et al., 2003).

JNJ-37822681 is a novel, highly selective, fast-dissociating D_2 dopamine receptor antagonist in development as a potential treatment for schizophrenia (Langlois et al., 2012). JNJ-37822681 has moderate affinity for the dopamine D_2 receptor and low affinity for D_1 and D_3 dopamine, serotonin, histamine, and adrenalin receptors (Langlois et al., 2010). In a previous radioligand binding assay, the dissociation rate of JNJ-37822681 from dopamine D_{2L} receptor was similar to that of clozapine and significantly faster than that of haloperidol, risperidone and paliperidone (Langlois et al., 2010). JNJ-37822681 was selected for development based on the theory that rapid dissociation from the D_2 receptor would reduce the risk of extrapyramidal side effects (Kapur and Seeman, 2001). Unlike many atypical antipsychotics (including olanzapine), the D_2 receptor-selective antagonistic profile of JNJ-37822681 may limit adverse effects associated with off-target receptor binding (Schmidt et al., 2012). Additionally, with the lack of the need for titration, treatment with JNJ-37822681 may translate into rapid onset of efficacy and enhanced tolerability (Kapur and Seeman, 2001).

Recently, results from a 12-week, double-blind, randomised, parallel-group, placebo- and active-controlled, dose–response study (Schmidt et al., 2012) demonstrated that JNJ-37822681 has a rapid, robust efficacy at week 6 in patients with an acute exacerbation of schizophrenia. In this report we describe results from a post hoc analysis that was conducted to investigate whether early onset of efficacy (within 1–2 weeks) is a reliable predictor of a sustained response (at week 6) for JNJ-37822681, and also whether other factors, including demographic and clinical variables influence the outcome.

2. Experimental procedures

2.1. Study population

The inclusion and exclusion criteria for the study are reported in detail elsewhere (Schmidt et al., 2012). Briefly, patients aged between 18 and 65 with body mass index (BMI) $\leq$40 kg/m^2, and diagnosed with schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] criteria) for at least 1 year before screening, experiencing an acute exacerbation of less than 6 months duration, with Positive and Negative Syndrome Scale (PANSS) total score between 60 and 120 (inclusive) at baseline were enroled (Kay et al., 1987). Patients were excluded if they had a DSM-IV axis I diagnosis other than schizophrenia; had never been treated with an antipsychotic or had a history of lack of response to antipsychotic therapy when acutely psychotic; had previously used clozapine for the indications of treatment resistance or reduction of suicidal risk; or had a history of any significant or unstable disease including diabetes.

2.2. Study design

This double-blind, placebo- and active-controlled study was conducted between September 2008 and February 2010 at 59 sites in 10 countries (Bulgaria, Estonia, Korea, Lithuania, Malaysia, Romania, Russia, South Africa, Taiwan and Ukraine) (Schmidt et al., 2012). Briefly, the study consisted of a 21-day screening period followed by a 12-week double-blind treatment phase consisting of an acute treatment phase and continuation phase of 6-weeks duration each. Patients were randomly