Journal of Psychiatric Research 53 (2014) 14–22

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A 6-week randomized, double-blind, placebo-controlled, comparator referenced trial of vabicaserin in acute schizophrenia

Joan H.Q. Shen [a], Yonggang Zhao [b], Sharon Rosenzweig-Lipson [c], Danielle Popp [d], Janet B.W. Williams [d,e,*], Earl Giller [d], Michael J. Detke [f,g], John M. Kane [h,i]

[a] Hengrui Medicine Co., Ltd, Shanghai, China
[b] Skyview Research, Pennsylvania, USA
[c] IVS Pharma Consulting, USA
[d] MedAvante Inc, Hamilton, NJ, USA
[e] College of Physicians and Surgeons, Columbia University, USA
[f] Detke Biopharma Consulting LLC, Carmel, IN, USA
[g] Indiana University School of Medicine, USA
[h] The Zucker Hillside Hospital, Glen Oaks, NY, USA
[i] The Albert Einstein College of Medicine, Bronx, NY, USA

ARTICLE INFO

Article history:
Received 8 February 2013
Received in revised form
28 January 2014
Accepted 13 February 2014

Keywords:
Clinical trial
Schizophrenia
Vabicaserin
Olanzapine
Placebo
Central rater

ABSTRACT

Vabicaserin, a potent 5-HT2C receptor agonist, decreases nucleus accumbens extracellular dopamine levels in rats, without affecting striatal dopamine, indicating mesolimbic selectivity. This is the first study of efficacy, safety and tolerability of vabicaserin in adults with acute schizophrenia. Three hundred fourteen hospitalized subjects were randomized to: Vabicaserin 200 or 400 mg/day, olanzapine 15 mg/day or placebo. Central raters assessed the PANSS and CGI-S. Site raters performed the BPRS and CGI-I. Central rated PANSS Positive (PANSS-PPS) was the primary endpoint. Two hundred eighty-nine subjects were included in the mITT efficacy analysis. Vabicaserin was well tolerated with no major safety concerns. Olanzapine, but not vabicaserin, caused weight gain. Vabicaserin 200 mg/day and olanzapine demonstrated significant improvement at week 6 vs. placebo on PANSS-PSS. A non-significant decrease vs. placebo was observed for 400 mg/day. Both vabicaserin groups demonstrated significant improvement over baseline on PANSS Negative while placebo worsened. Vabicaserin 200 mg/day and olanzapine demonstrated significantly greater improvement over placebo on PANSS Total whereas 400 mg/day showed a trend toward improvement. There was no significant improvement vs. placebo for either vabicaserin group on site-rated BPRS. Vabicaserin 200 mg/day and olanzapine demonstrated significant improvement vs. placebo on CGI-I and CGI-S but not 400 mg/day vabicaserin. Vabicaserin demonstrated efficacy on primary and secondary endpoints at 200 mg/day, but not at 400 mg/day which showed a trend for efficacy. The 200 mg/day vabicaserin group achieved proof of concept using central ratings. Both vabicaserin doses were well tolerated with no significant safety signals and no weight gain.

Trial Registration: clinicaltrials.gov.
Identifier: NCT00265551.

1. Introduction

Vabicaserin hydrochloride is a novel 5-HT2C agonist; this class of compounds has therapeutic potential in a wide range of psychiatric disorders, as evidenced through a number of pre-clinical animal models (Siuciak et al., 2007; Wang et al., 2008). Unlike most agents currently developed for the treatment of schizophrenia, vabicaserin does not involve directly targeting dopamine receptors and has *in vitro* functional selectivity for 5-HT2C without impacting 5-HT2A or 5-HT2B receptors (Dunlop et al., 2011). Vabicaserin is effective in multiple animal models of antipsychotic activity including attenuation of apomorphine-induced climbing, decreased conditioned avoidance responding, reversal of PCP and amphetamine-induced hyperactivity, and is effective in prepulse inhibition (Marquis et al., 2006; Rosenzweig-Lipson et al., 2012).

* Corresponding author. SVP, Global Science, MedAvante, Inc., 100 American Metro Blvd. #106, Hamilton, NJ 08619, USA. Tel.: +1 609 528 9472; fax: +1 609 528 9401.
E-mail address: jwilliams@medavante.com (J.B.W. Williams).

http://dx.doi.org/10.1016/j.jpsychires.2014.02.012
0022-3956/

Acute and chronic administration of vabicaserin decreases nucleus accumbens dopamine without affecting striatal dopamine, which is indicative of mesolimbic selectivity (Marquis et al., 2006; Rosenzweig-Lipson et al., 2012). This profile is consistent with potential efficacy in the treatment of psychotic symptoms of schizophrenia. Chronic administration of vabicaserin significantly decreases the number of spontaneously active mesocorticolimbic dopamine neurons without affecting nigrostriatal dopamine neurons, consistent with the effects of atypical antipsychotics (Rosenzweig-Lipson et al., 2012). Unlike atypical antipsychotics, acute administration of vabicaserin is also selective for mesocorticolimbic dopamine neurons, suggesting that this compound could have a rapid onset of action.

Vabicaserin also increases medial prefrontal cortex glutamate and acetylcholine which is suggested to be associated with improvements in cognitive function (Rosenzweig-Lipson et al., 2007). Results from completed pre-clinical studies suggest that 5-HT2C agonists could be effective in improving mood disorders and cognitive impairments associated with schizophrenia, without producing extrapyramidal side effects or weight gain (Rosenzweig-Lipson et al., 2012). Therefore, vabicaserin offers the possibility of a new antipsychotic medication with broader efficacy (e.g., cognitive symptoms) as well as improved safety and tolerability (Rosenzweig-Lipson et al., 2012; Shen et al., 2011a,b).

This study aims to 1) examine the efficacy of vabicaserin hydrochloride in adult subjects with acute schizophrenia, and 2) compare two different methodological approaches (blinded independent central raters and traditional site raters) for the assessment of symptom severity in CNS clinical trials. This was the first randomized controlled trial to use central raters in a study of treatments for schizophrenia (Shen et al., 2008).

2. Methods

2.1. Subjects

Adult subjects ($n = 289$) with acute exacerbation of schizophrenia participated in a six-week randomized, double-blind, placebo-controlled, comparator-referenced, multicenter parallel-group trial. Subjects included 209 men and 80 women ranging in age from 20 to 63 years ($M = 40.2$, SD = 10.3) at 32 sites located in the United States ($n = 28$) and India ($n = 4$). Subjects were predominately African American (64.4%; $n = 186$), Caucasian (30.1%; $n = 87$) or Asian (3.5%; $n = 10$). Subjects' mean height and weight at baseline were 173.8 cm and 90 kg. The study was conducted from December 2005 to April 2007. All subjects were hospitalized for acute schizophrenia (mean duration of current episode = 108.0 days; SD = 425.7). Subjects remained hospitalized for a minimum of 4 weeks during the double-blind phase of the study. Subjects were discharged from the hospital either after the day 28 assessment or scheduled evaluation thereafter, based on the investigator's judgment and subject responses to the Readiness Discharge Questionnaire (Dunlop et al., 2011).

2.2. Inclusion/exclusion criteria

In order to be included in the study, all subjects were required to have a PANSS total score ≥ 70 and ≤ 120, a PANSS Positive Symptoms Subscale score ≥ 20, and scores of ≥ 4 on at least two of the following PANSS items: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. Further, subjects must have had CGI-S scores ≥ 4 at both screening and baseline.

Subjects were excluded for having a current Axis I primary psychiatric diagnosis other than schizophrenia, being considered a significant suicide risk by the investigator or having a CDSS score of 3 on the suicide item. Subjects were also excluded for a current diagnosis or history of substance dependence. Further, subjects were not enrolled if they had used olanzapine within the past 30 days or had a known history of resistance to antipsychotic treatment.

2.3. Procedure

The diagnosis of schizophrenia was made by site investigators using the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002). After a one-week washout period, subjects were assigned to 1 of 4 treatment arms: 200 mg/day vabicaserin ($n = 82$), 400 mg/day vabicaserin ($n = 77$), olanzapine 15 mg/day (active comparator; $n = 77$), or placebo ($n = 77$). Randomization was performed by the Legacy Wyeth T&RS Randomization System using blocked randomization (block size = 4). The Legacy Wyeth Computerized Randomization/Enrollment (CORE) system was used to implement the random allocation sequence. The randomization statistician generated the random sequence, sites enrolled patients, and the Legacy Wyeth CORE system was used to assign participants to interventions.

Subjects received morning and evening treatment at the same time each day, either with or without food depending on individual tolerability. The following adjunctive medications were permitted during the study for the control of agitation, insomnia or extrapyramidal symptoms: lorazepam, clorazepate dipotassium, benztropine, biperiden, trihexyphenidyl HCl, zaleplon, and zolpidem. Treatment with any other anxiolytics, antiparkinsonian agents, or sedative-hypnotics was prohibited. Additional prohibited treatments included: antidepressants, MAOIs, analgesics (opioid), anticonvulsants, electroconvulsive therapy, psychostimulants or sympathomimetics, psychotropic drugs or substances, psychotherapy, lithium, barbiturates, drugs known to influence dopamine or serotonin neurotransmission, and drugs known to prolong the QT/QTc interval.

Independent central raters who were blinded to study design, inclusion criteria, and visit number administered the Structured Clinical Interview for the PANSS (SCI-PANSS; Kay et al., 1987) and the Clinical Global Impressions-Severity scale (CGI-S; Guy, 1976) remotely via live, videoconferencing at screening. A member of the site staff, who did not perform any efficacy assessments at that visit, remained in the room with the subject during the remote assessment. Interviews were conducted at baseline and each of the six weekly post-baseline visits (see Shen et al., 2008 for information on central raters' education and experience). Several studies have demonstrated high reliability between face-to-face and videoconference administration of psychiatric scales in subjects with schizophrenia (e.g., Yoshino et al., 2001; Zarate et al., 1997). Central raters were provided information on the subject's behavior from an informant who had observed the subject over the week prior to the interview. Typically, there was a different central rater at each visit. Central rater symptom severity assessments determined subject eligibility.

After central raters completed their assessments, site raters performed the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) and the CGI-I the same day. Site raters, blinded to treatment but unblinded to inclusion criteria, study design, and visit number (as is typical in double-blind studies) performed the BPRS to avoid subject fatigue associated with undergoing two consecutive PANSS interviews. To allow for comparisons between site and central raters, a BPRS total score was derived from the central raters' PANSS assessment. The PANSS includes all items of the BPRS along with an additional 12 items designed to assess broader psychopathology (Furukawa et al., 2011). Derived BPRS