P8-022

Efficacy of Cariprazine in Negative, Cognitive, and Social Function Symptoms in Schizophrenia: Post Hoc Analysis of a Randomized, Controlled Trial

Andrew J Cutler, MD,[1] Suresh Durgam, MD,[2] Kaifeng Lu, PhD,[2] István Laszlovszky, PharmD, PhD,[3] Willie Earley, MD[2]

[1]Meridian Research, Inc., Bradenton, FL, USA; [2]Allergan, Inc., Jersey City, NJ, USA; [3]Gedeon Richter Plc, Budapest, Hungary

Scan to obtain PDF of poster

ABSTRACT

Introduction: Antipsychotics are generally effective in treating the positive symptoms of schizophrenia, but negative symptoms and cognitive deficits are difficult to treat and may contribute to poor social functioning. Cariprazine, a potent dopamine D_3/D_2 receptor partial agonist with preferential binding to D_3 receptors, is approved for the treatment of schizophrenia. It has shown efficacy in a broad range of schizophrenia symptoms in clinical trials. This post hoc analysis of a Phase 3 placebo- and active-controlled trial (NCT01104766) evaluates cariprazine on Positive and Negative Syndrome Scale (PANSS)-derived subscales related to negative symptoms, cognition, and social functioning in patients with acute exacerbation of schizophrenia.

Methods: A total of 604 patients were randomized to 6 weeks of double-blind treatment (placebo=149, cariprazine 3 mg/d=151, cariprazine 6 mg/d=154, aripiprazole 10 mg/d=150). Efficacy was analyzed using change from baseline in PANSS negative subscale score and PANSS-derived cognitive (P2, N5, N7, G10, G11) and prosocial (P3, P6, N2, N4, N7, G16) factor scores.

Results: The least squares mean difference (LSMD) was statistically significant in favor of cariprazine over placebo in PANSS negative (3 mg/d=-1.4 [95% CI: -2.4, -0.4], *P*=.0068; 6 mg/d=-1.7 [95% CI: -2.7, -0.7], *P*=.0009), cognitive (3 mg/d=-1.2 [95% CI: -1.9, -0.5], *P*=.0005; 6 mg/d=-1.2 [95% CI: -1.9, -0.6], *P*=.0004), and prosocial (3 mg/d=-1.4 [95% CI: -2.5, -0.4], *P*=.0070; 6 mg/d=-2.2 [95% CI: -3.2, -1.1], *P*<.0001) scores. In PANSS negative score, significant improvement was seen for both cariprazine doses versus placebo by Week 1 (*P*<.05). In PANSS cognitive score, significant improvement was seen by Week 2 for cariprazine 6 mg/d (*P*<.05) and Week 3 for 3 mg/d (*P*<.01). In PANSS prosocial score, significant improvement was seen by Week 1 for cariprazine 6 mg/d and Week 3 for 3 mg/d (*P*<.05 for both). Early separation from placebo for both cariprazine doses on PANSS negative, cognitive, and prosocial scores was maintained through Week 6. LSMDs for aripiprazole versus placebo were statistically significant on PANSS negative (-1.2 [95% CI: -2.2, -0.2], *P*=.0152), cognitive (LSMD=-1.0 [95% CI: -1.6, -0.3], *P*=.0047), and prosocial (LSMD=-1.3 [95% CI: -2.4, -0.3], *P*=.0099) scores. Significant improvement was seen by Week 3 on PANSS cognitive scores (*P*<.001) and by Week 2 on negative (*P*<.05) and prosocial (*P*<.01) scores; significant differences were maintained through Week 6.

Conclusions: Cariprazine 3 and 6 mg/d demonstrated significant and sustained efficacy versus placebo within 1 to 3 weeks of treatment initiation across PANSS negative, cognitive, and prosocial domains. Results suggest that cariprazine may be beneficial in improving negative and cognitive symptoms as well as social functioning in patients with acute exacerbation of schizophrenia.

INTRODUCTION

- Positive symptoms of schizophrenia can be successfully treated with atypical antipsychotics; however, negative symptoms and cognitive impairment are difficult to treat and can have a detrimental effect on psychosocial function[1,2]
- Given the impact of negative and cognitive symptoms on social functioning, new treatments are needed that improve outcomes in these symptom domains since many patients with schizophrenia live in community settings where adequate functioning is required to support quality of life
- Cariprazine, a potent D_3/D_2 receptor partial agonist with preferential binding to D_3 receptors, is approved for the treatment of schizophrenia in adult patients at a recommended dose of 1.5-6 mg/d

OBJECTIVE

- The objective of this post hoc analysis was to evaluate the efficacy of cariprazine in improving PANSS negative and PANSS-derived cognitive and prosocial factor scores in patients with schizophrenia

METHODS

Study Design

- Data were analyzed from a 6-week, double-blind, Phase 3, randomized, placebo- and active-controlled trial (NCT01104766)[3] in adult patients with acute exacerbation of schizophrenia
- Patients were randomized (1:1:1:1) to receive placebo, cariprazine 3 mg/d, cariprazine 6 mg/d, or aripiprazole 10 mg/d (included for assay sensitivity)
- Male or female inpatients (18 to 60 years, inclusive) met DSM-IV-TR criteria for schizophrenia for ≥1 year with at least 1 psychotic episode that required hospitalization or change in antipsychotic treatment during the past year
- Current psychotic episode was <2 weeks; patients had a PANSS total score ≥80 and ≤120 and a score of ≥4 on at least 2 of the PANSS positive symptoms of delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness/persecution

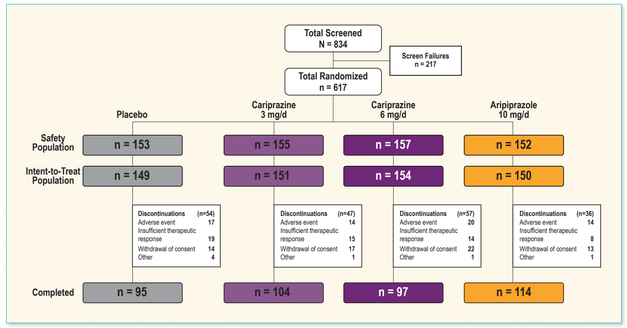
Data Analysis

- Efficacy was analyzed using change from baseline in PANSS negative subscale score (items N1-N7) and PANSS-derived cognitive and prosocial factor scores in the intent-to-treat population (ITT; all patients who received ≥1 dose of study medication and had ≥1 post-baseline PANSS assessment)
  - PANSS items included in the cognitive factor are P2: conceptual disorganization, N5: difficulty in abstract thinking, N7: stereotyped thinking, G10: disorientation, G11: poor attention
  - PANSS items included in the prosocial factor are P3: hallucinatory behavior, P6: suspiciousness/persecution, N2: emotional withdrawal, N4: passive/apathetic social withdrawal, N7: stereotyped thinking, G16: active social avoidance
- Data were assessed using a mixed-effects model for repeated measures (MMRM)

RESULTS

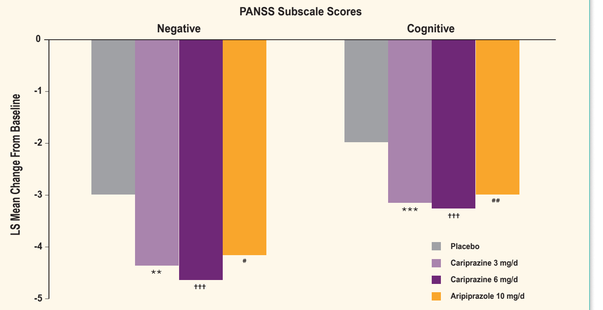
- A total of 604 patients were included in the ITT population (**Figure 1**)
- Patient disposition and baseline characteristics were similar among treatment groups and have been previously described[3]

Figure 1. Patient Populations and Disposition



- Mean changes from baseline to Week 6 in PANSS negative score and PANSS-derived cognitive factor score are shown in **Figure 2**
  - Statistically significant differences in favor of cariprazine 3 and 6 mg/d versus placebo were seen on both efficacy measures at Week 6
    - On the PANSS negative subscale score, significant improvement for cariprazine 3 mg/d versus placebo was seen at Week 1 (*P*=.0468) and from Week 3 through Week 6 (each visit, *P*<.05); significant improvement was seen for cariprazine 6 mg/d versus placebo at Week 1 (*P*=.0168) and was maintained through Week 6 (each visit, *P*<.05)
    - On the PANSS-derived cognitive score, significant improvement versus placebo was seen by Week 2 (*P*=.0321) for cariprazine 6 mg/d and by Week 3 (*P*=.0014) for cariprazine 3 mg/d; improvement was maintained through Week 6 for both doses (each visit, *P*<.05)
  - Aripiprazole also showed significantly greater improvement than placebo in PANSS negative subscale score starting at Week 2 (*P*=.0130) and in PANSS-derived cognitive factor score starting at Week 3 (*P*=.0007); significant differences were maintained through Week 6 (each visit, *P*<.05)

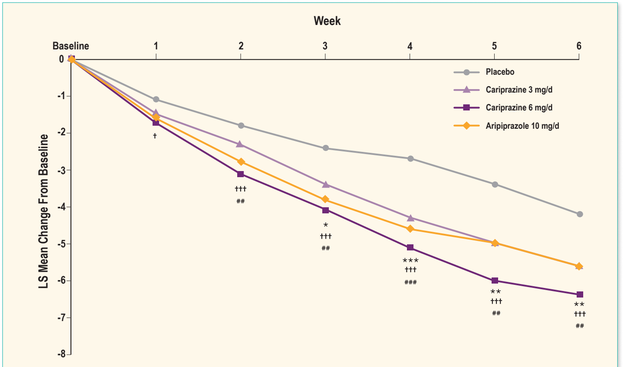
Figure 2. Mean Change From Baseline to Week 6 in PANSS Negative and Cognitive Scores (ITT Population, MMRM)[a]



[a]Change over time on the PANSS negative and PANSS cognitive subscales has been previously described.[3]
P values are from an MMRM analysis with treatment group, pooled study center, visit, and treatment group-by-visit interaction as factors, and baseline value and baseline-by-visit interaction as covariates.
ITT, intent-to-treat; MMRM, mixed-effects model for repeated measures.
Cariprazine 3 mg/d vs placebo: **P*<.01, ***P*<.001; cariprazine 6 mg/d vs placebo: †††*P*<.001; aripiprazole 10 mg/d vs placebo: #*P*<.05; ##*P*<.01.

- For the PANSS-derived prosocial factor score (**Figure 3**), significant improvement versus placebo was seen by Week 1 for cariprazine 6 mg/d and by Week 3 for cariprazine 3 mg/d; a significant difference was maintained through Week 6
- Aripiprazole also showed significant improvement versus placebo from Week 2 through Week 6

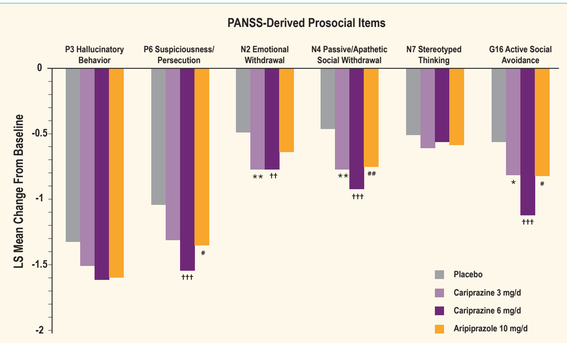
Figure 3. Mean Change From Baseline in PANSS Prosocial Score by Week (ITT Population, MMRM)



P values are from an MMRM analysis with treatment group, pooled study center, visit, and treatment group-by-visit interaction as factors, and baseline value and baseline-by-visit interaction as covariates.
ITT, intent-to-treat; MMRM, mixed-effects model for repeated measures.
Cariprazine 3 mg/d vs placebo: **P*<.05, ***P*<.01, ****P*<.001; cariprazine 6 mg/d vs placebo: †*P*<.05, †††*P*<.001; aripiprazole 10 mg/d vs placebo: ##*P*<.01, ###*P*<.001.

- Cariprazine 6 mg/d was significantly superior to placebo on 4 of 6 PANSS-derived prosocial items (**Figure 4**); cariprazine 3 mg/d and aripiprazole were significantly superior to placebo on 3 of 6 PANSS-derived prosocial items

Figure 4. Mean Change From Baseline to Week 6 in PANSS-Derived Prosocial Items (ITT population, MMRM)



P values are from an MMRM analysis with treatment group, pooled study center, visit, and treatment group-by-visit interaction as factors, and baseline value and baseline-by-visit interaction as covariates.
ITT, intent-to-treat; MMRM, mixed-effects model for repeated measures.
Cariprazine 3 mg/d vs placebo: **P*<.05, ***P*<.01; cariprazine 6 mg/d vs placebo: ††*P*<.01, †††*P*<.001; aripiprazole 10 mg/d vs placebo: #*P*<.05, ##*P*<.01.

CONCLUSIONS

- Treatment with cariprazine versus placebo resulted in significant and sustained improvement by Week 3 in PANSS negative subscale and PANSS-derived cognitive subscale scores
- Improving negative and cognitive symptoms may be related to concurrent improvement in measures of prosocial functioning
  - Cariprazine 3 and 6 mg/d also demonstrated efficacy on the PANSS-derived prosocial factor score, with significant advantage versus placebo in 3 of 6 (3 mg/d) and 4 of 6 (6 mg/d) PANSS-derived prosocial items
  - Significant improvement in each score was generally seen earlier with cariprazine 6 mg/d than 3 mg/d
  - The cariprazine 6 mg/d group compared with the 3 mg/d group or the aripiprazole group showed the largest treatment effects versus placebo
- Cariprazine may have broad effects across multiple symptom domains, including negative and cognitive symptoms; improvements in these symptom domains may contribute to improved psychosocial functioning in patients with acute exacerbations of schizophrenia

REFERENCES

1. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull*. 2000;26(1):119-136.
2. Hunter R, Barry S. Negative symptoms and psychosocial functioning in schizophrenia: neglected but important targets for treatment. *Eur Psychiatry*. 2012;27(6):432-436.
3. Durgam S, Cutler AJ, Lu K, *et al*. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015;76(12):e1574-1582.

DISCLOSURES

Dr. Cutler has received research support from Alkermes, AstraZeneca, Forest Laboratories, LLC, Braeburn, Forum, Janssen (Johnson & Johnson), Eli Lilly, Lundbeck, Neurocrine, Novartis, Otsuka, Pfizer, Reckitt Benckiser, Sunovion, Takeda, and Vanda; served as a consultant for Alkermes, AstraZeneca, Forest Laboratories, LLC, Braeburn, Forum, Janssen (Johnson & Johnson), Jazz, Eli Lilly, Lundbeck, Neurocrine, Novartis, Otsuka, Pfizer, Sunovion, Takeda, Teva, and Vanda; and served as a speaker for Alkermes, AstraZeneca, Forest Laboratories, LLC, Janssen (Johnson & Johnson), Jazz, Eli Lilly, Lundbeck, Novartis, Otsuka, Pfizer, Sunovion, Takeda, Teva, and Vanda. Drs. Earley, Durgam and Lu are employees of Allergan, Inc. Dr. Laszlovszky is an employee of Gedeon Richter Plc. Writing and editorial assistance was provided by Prescott Medical Communications Group (Chicago, IL) and funded by Allergan, Inc. (Irvine, CA). All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

To obtain a PDF of this poster:
- **Scan the QR code**
  OR
- **Visit www.allergancongressposters.com/771597**

Charges may apply.
No personal information is stored.

Supported by funding from Forest Research Institute, Inc., an Allergan affiliate, and Gedeon Richter Plc