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Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial

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Summary

Background **Although predominant negative symptoms of schizophrenia can be severe enough to cause persistent impairment, effective treatment options are lacking. We aimed to assess the new generation antipsychotic cariprazine in adult patients with predominant negative symptoms.**

Methods **In this randomised, double-blind, phase 3b trial, we enrolled adults aged 18–65 years with long-term (>2 year), stable schizophrenia and predominant negative symptoms (>6 months) at 66 study centres (mainly hospitals and university clinics, with a small number of private practices) in 11 European countries. Patients were randomly assigned (1:1) by an interactive web response system to 26 weeks of monotherapy with fixed-dose oral cariprazine (3 mg, 4·5 mg [target dose], or 6 mg per day) or risperidone (3 mg, 4 mg [target dose], or 6 mg per day); previous medication was discontinued over 2 weeks. The primary outcome was change from baseline to week 26 or end of treatment on the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) analysed in a modified intention-to-treat population of patients who had follow-up assessments within 5 days after last receipt of study drugs with a mixed-effects model for repeated measures. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with EudraCT, number 2012-005485-36.**

Findings **Between May 27, 2013, and Nov 17, 2014, 533 patients were screened and 461 (86%) patients were randomised to treatment (230 for cariprazine and 231 for risperidone); 460 were included in the safety population (one patient discontinued before study drug intake). 227 (99%) of 230 patients in the cariprazine group and 229 (99%) of 230 patients in the risperidone group were included in the modified intention-to-treat population (178 [77%] in each group completed 26 weeks of treatment). Mean daily doses were 4·2 mg (SD 0·6) for cariprazine and 3·8 mg (0·4) for risperidone. Treatment-emergent adverse events (eg, insomnia, akathisia, worsening of schizophrenia, headache, anxiety) were reported in 123 (54%) patients treated with cariprazine and 131 (57%) patients treated with risperidone. Use of cariprazine led to a greater least squares mean change in PANSS-FSNS from baseline to week 26 than did risperidone (−8·90 points for cariprazine *vs* −7·44 points for risperidone; least squares mean difference −1·46, 95% CI −2·39 to −0·53; p=0·0022; effect size 0·31). One patient in the risperidone group died of a cause regarded as unrelated to treatment.**

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Interpretation **Our results support the efficacy of cariprazine in the treatment of predominant negative symptoms of schizophrenia.**

Funding **Gedeon Richter Plc.**

Introduction

Negative symptoms of schizophrenia include the absence or reduction of normal behaviour and function in patients with schizophrenia; the symptoms are strongly associated with long-term morbidity, poor psychosocial functioning, considerable social and economic costs, and high levels of unemployment. Primary and enduring negative symptoms (ie, blunted affect, anhedonia, avolition, asociality, and alogia) are a core feature of schizophrenia and patients with these symptoms account for a distinct clinical subpopulation.[1] These symptoms persist during periods of clinical stability, are considered only marginally responsive to treatment with antipsychotic drugs, and can be severe enough to interfere with normal functions.[1, 2] By contrast, secondary negative symptoms are considered to happen as a consequence of positive symptoms, depression, or side-effects of antipsychotic treatments.[1] Although second-generation antipsychotics have modest efficacy in secondary negative symptoms, improvement occurs in tandem with improvements in positive, depressive, or extrapyramidal symptoms.[1] The dearth of available treatments for predominant negative symptoms in schizophrenia is a crucially important unmet medical need.

Cariprazine, a dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors, is approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adults. Cariprazine differs from all available antipsychotics because it has almost 10 times greater affinity for D3 than D2 receptors in vitro,[3] and high and balanced in-vivo occupancy of both D2 and D3 receptors in rats[4] and human beings.[5] The dopamine D3 receptor is thought to be important in modulating mood and cognition,[6, 7, 8] and preclinical evidence suggests that cariprazine may be beneficial in treating negative symptoms, dysphoria, and cognitive impairment associated with schizophrenia.[9, 10, 11, 12] These pharmacodynamic properties, as well as affinity for the serotonin 5-HT1A receptor, provided a non-clinical rationale to investigate cariprazine monotherapy in the treatment of patients with predominant negative symptoms in schizophrenia. Post-hoc analyses of two short-term efficacy trials that assessed patients in predominant negative symptom subgroups provided further positive signals.[13, 14] In this clinical trial, we aimed to assess the clinical efficacy and safety of cariprazine in patients with predominant negative symptoms.

Research in context

Evidence before this study

We searched PubMed and Embase with the keywords schizophrenia, negative symptoms, antipsychotics, atypical antipsychotics, and atypical antipsychotic monotherapy; randomised controlled trials without date restrictions that were published in English were considered up to Jan 19, 2016. Our search yielded few prospectively designed trials of antipsychotic monotherapy in patients who were well characterised as having schizophrenia with predominant negative symptoms. Negative symptoms in schizophrenia are associated with considerable morbidity and functional impairment, and no consistently effective treatments are available. As such, negative symptoms are regarded as a valid target for treatment interventions and drug development by agencies in Europe and the USA. The pharmacodynamics properties of cariprazine and its active metabolites, especially its higher affinity and greater selectivity for dopamine D3 than D2 receptors, as well as its considerable affinity for the 5-HT1A receptor, supported our decision to investigate the potential for efficacy in specific symptom domains of schizophrenia, including primary negative symptoms. Post-hoc analyses of two 6-week double-blind, placebo-controlled and active-controlled studies of cariprazine treatment in patients with acute exacerbation of

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schizophrenia showed that patients with high baseline scores for negative symptoms had greater improvement in negative symptoms when they were treated with cariprazine compared with placebo, risperidone, or aripiprazole. Because these results suggested that cariprazine had the potential for efficacy in negative symptoms, a prospectively designed study was done in clinically stable patients identified as having predominant negative symptoms.

Added value of this study

This study adds to the existing evidence for antipsychotic drugs in the treatment of predominant negative symptoms antipsychotic effects, four of nine second-generation drugs (risperidone, amisulpride, clozapine, and olanzapine) were more effective than first-generation antipsychotics in the treatment of negative symptoms; although the included studies were not done in patients with predominant negative symptoms, the authors concluded that efficacy in negative symptoms cannot be considered a central characteristic of atypicality. Amisulpride, the most widely studied antipsychotic in patients with predominant negative symptoms, is indicated for negative symptoms in several European countries. While the studies of amisulpride are interesting and informative, especially in a therapeutic area with continued unmet medical need, most of the evidence showing efficacy for amisulpride is versus placebo; given this limitation and other methodological differences between the amisulpride studies and the cariprazine study, it is not possible to make meaningful comparisons between treatments. Generally, evidence that any antipsychotic drug is effective in patients with predominant negative symptoms is insufficient. The results of our trial challenge this conclusion. Furthermore, although adjunctive treatment of negative symptoms is common, evidence that supports the concomitant use of antipsychotic drugs with other mechanisms of action (eg, antidepressants, glycine transport inhibitors, and glutamatergic compounds) is inconsistent and clinical benefit has not been shown.

Implications of all the available evidence

Given the lack of widely approved and clinically meaningful treatments, as well as the considerable unmet medical need in this vulnerable patient population, cariprazine has the potential to change clinical practice by providing a treatment option for patients with predominant negative symptoms of schizophrenia. Treatment with cariprazine monotherapy not only improved predominant negative symptoms in patients with schizophrenia, but the effect was also clinically meaningful, as shown by improvement in patient functioning.

Methods

Study design and participants

This phase 3b randomised, double-blind trial was done at 66 study centres in 11 European countries (Bulgaria, Croatia, Czech Republic, France, Hungary, Poland, Romania, Serbia, Spain, Russia, and Ukraine).

To be screened for the study, patients had to be known to investigators directly or through referral; a psychiatric history had to be available to ensure that patients had predominant negative symptoms and low levels of positive symptoms, and were therefore suitable for participation. Patients eligible for the study were adults aged 18–65 years who had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria (confirmed by the Structured Clinical Interview for DSM-IV-TR, Clinical Trials Version), with onset occurring at least 2 years before screening. Patients had to be in a stable condition for at least 6 months before screening (ie, no psychiatric hospital admissions, acute exacerbations, or imprisonments) and meet the following clinical criteria: predominant negative symptoms for at least 6 months (based on medical records/investigator judgment), Positive and Negative Syndrome Scale

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factor score for negative symptoms (PANSS-FSNS)[15] of 24 or more, and score of 4 or more on at least two of three core negative PANSS items (blunted affect, passive or apathetic social withdrawal, lack of spontaneity, and flow of conversation) at screening and during a lead-in period. Additionally, patients were required to have a PANSS-FSNS score that diverged less than 25% from the screening score during a lead-in period.

Patients were excluded because of a current DSM-IV-TR axis I disorder other than schizophrenia or because of other conditions that could have interfered with the study (appendix); history of non-response to an adequate trial of risperidone for the treatment of a psychotic episode and treatment with risperidone within 6 weeks of screening were also exclusionary. Patients whose condition was determined to be unstable and those with a PANSS factor score for positive symptoms (PANSS-FSPS)[16] of more than 19 or a score increase of 25% or more during a lead-in period were ineligible. To ensure that improvements in negative symptoms were not secondary to improvements in other psychopathological domains (ie, pseudospecific), patients were excluded for positive symptoms (score ≥4 on two or more positive PANSS items: delusions, hallucinatory behaviour, grandiosity, suspiciousness, or unusual thought content), moderate or severe depressive symptoms (Calgary Depression Scale for Schizophrenia [CDSS] total score >6), or clinically relevant parkinsonism (investigator judged or score >3 on the sum of the first eight items of the Simpson-Angus Scale [SAS]). Treatment with additional psychotropic medications was prohibited with few exceptions, as prespecified in the protocol. The clinical study protocol was approved by nine central and 37 local independent ethics committees in relation to the 66 sites that recruited at least one patient; the study was done in accordance with good clinical practice guidelines and the principles of the International Conference on Harmonisation. All patients provided written informed consent.

Randomisation and masking

We sequentially assigned a unique identification number to each patient who gave consent. We used an interactive voice/web response system to monitor enrolment and drug allocation; study centres contacted the system at screening to identify the patient in the system and at the end of a lead-in period to assign a randomisation number (if randomisation criteria had been met). At randomisation, participants were randomly allocated (1:1) to once-daily cariprazine or risperidone. We masked the study to patients, investigators, and the funder; a list of patient randomisation codes identified each patient by identification and randomisation numbers. Masking codes were only broken in emergency situations for safety reasons; if the code was broken, the treatment was discontinued for the patient. The interactive system provider determined the block size and kept the size as information to be unmasked together with the randomisation codes. After database lock and the release of randomisation codes, we confirmed a block size of four. Cariprazine and risperidone capsules were identical in appearance through overencapsulation (Gedeon Richter Plc).

Procedures

The study consisted of a 4-week prospective lead-in period, during which the patient's current antipsychotic treatment remained unchanged, a 26-week double-blind treatment period, and a 2-week safety follow-up. The first part of the double-blind treatment consisted of a 2-week uptitration phase: from randomisation (day 0 of the treatment phase) to day 6, patients received 1·5 mg per day of cariprazine or 2 mg per day of risperidone; on days 7–13, patients in both treatment groups received 3 mg per day of their respective study drug; and on day 14, patients received the target dose of cariprazine (4·5 mg per day) or risperidone (4 mg per day). Antipsychotic treatment taken during the lead-in period was downtitrated during this period and discontinued on day 14; to decrease the severity of withdrawal effects or impending deterioration, the investigator could prolong downtitration for a maximum of 4 weeks. The second part of the double-blind treatment was a 24-week continuation phase; target doses were maintained except in cases of poor tolerability

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or impending psychotic deterioration. Decrease or increase from the target dose could occur only once for each modification during the continuation phase. We chose the accepted fixed doses of cariprazine (3 mg, 4·5 mg, or 6 mg per day) and risperidone (3 mg, 4 mg, or 6 mg per day) in accordance with the respective product labels. The target dose for cariprazine (4·5 mg per day) was based on data from completed studies (NCT01104766 and NCT00694707) in patients with schizophrenia; we selected the target dose for risperidone (4 mg day) to correspond to the usual daily dose for patients with stable schizophrenia and to minimise the occurrence of extrapyramidal symptoms.

Outcomes

The primary efficacy outcome was change in the PANSS-FSNS scores from randomisation to 26 weeks (or early termination). We assessed this outcome with the Structured Clinical Interview for the PANSS done during the double-blind study at weeks 1, 2, 3, 4, 6, 10, 14, 18, 22, and 26. The PANSS-FSNS consists of items N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (passive or apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G7 (motor retardation), and G16 (active social avoidance); a higher score indicates worse severity. The secondary efficacy outcome was the Personal and Social Performance Scale (PSP) total score measured at weeks 6, 10, 14, 18, 22, and 26; higher score indicates better functioning.

Investigators assessed additional efficacy outcomes and safety parameters, including adverse event reports and clinical laboratory values (appendix). To verify that changes were specific to negative symptom improvement and not pseudospecific, we assessed the change from baseline at endpoint on the PANSS-FSPS (the sum of items P1, P3, P5, P6, and G9), CDSS total score, and the first eight items of the SAS. To minimise potential for inter-rater variability, only clinically experienced and certified raters who met predetermined training requirements administered the rating instruments. Of the 142 certified raters who rated at least once, 140 (99%) were board certified psychiatrists and two (1%) were medical doctors trained in the specific scales they administrated.

Statistical analysis

We calculated that a sample size of 210 patients per treatment group would provide at least 90% power to detect an effect size of 0·25 at a two-sided α-level of 0·05 for statistical significance, assuming a treatment difference of 2·25 points (calculated backwards from the effect size) and a pooled SD of 9 points, a correlation coefficient of 0·2 between repeated measurements, and 10% attrition rate.

Safety analyses were based on the safety population (all randomised patients who took at least one dose of the study drug). Efficacy analyses were based on a modified intention-to-treat population, which was defined as all patients in the safety population who had at least one PANSS-FSNS assessment after the start of double-blind treatment (baseline). We defined baseline values for safety and efficacy as the last available values recorded before the first dose of the double-blind study drug.

The primary analysis of change from baseline to endpoint (week 26 or early termination) in PANSS-FSNS used a mixed-effects model for repeated measures (MMRM) with treatment group, study centre, visit, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline value-by-visit interaction as covariates. An unstructured covariance matrix, which makes no assumptions about the variance of data, was used to model the covariance of within-patient scores. *F* tests were based on Kenward-Roger's adjusted denominator degrees of freedom; analysis was based on all postbaseline scores using observed cases without imputation of missing values (final assessment was omitted if the study drug had been stopped more than 5 days before assessment). For PSP total score (the secondary efficacy parameter), we analysed the change from

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baseline at endpoint with an MMRM similar to the one used for the primary efficacy parameter; analysis was only to be done if the result of the primary efficacy parameter was positive.

We did two sensitivity analyses, an ANCOVA using the last observation carried forward (LOCF) approach and a pattern-mixture model (PMM), to assess the robustness of MMRM results on the primary and secondary parameters. We analysed additional efficacy and pseudospecificity parameters with an MMRM similar to the one used for the primary analysis. We analysed PANSS-FSNS responder rates using a logistic regression model. Statistical tests were done with a two-sided α-level of 0·05 for statistical significance; between-treatment comparisons were reported with a 95% CI. See appendix for additional statistical analysis details.

Post-hoc sensitivity analyses were done to further characterise prespecified analyses: PANSS-FSNS and PSP total score effect sizes (Hedges' g), PANSS-FSNS decrease of 30% or more at endpoint, PSP total score change of more than 10 points, PSP category shift analysis, and Clinical Global Impressions (CGI) improvement. All other outcomes were prespecified by the study protocol.

Statistical analyses were produced with SAS version 9.3.1. No interim analyses were planned or done. This study is registered with EudraCT, number 2012-005485-36.

Role of the funding source

The funder was involved in the study design, collection (via contracted clinical investigator sites), analysis, and interpretation of data, and decided to submit for publication. Authors had full access to the study data and complete discretion in the analysis of data and writing of this report.

Results

The study was initiated on May 27, 2013, and last patient visit was completed on Nov 17, 2014. We randomly allocated 461 (86%) of 533 patients screened (figure 1), of whom one discontinued before receiving treatment (not included in the safety population of 230 per group) and four had their last PANSS measurement more than 5 days after their last dose of study medication (not included in the modified intention-to-treat group: 227 patients for cariprazine and 229 for risperidone). 104 (23%) of 460 patients prematurely discontinued (uptitration phase: eight [4%] of 230 for cariprazine and four [2%] of 230 for risperidone; continuation phase: 44 [19%] for cariprazine and 48 [21%] for risperidone). Baseline characteristics seemed balanced between groups (table 1).

Ten PANSS assessments were scheduled for each of the 460 patients after randomisation. A total of 4137 PANSS assessments were done. For the primary efficacy parameter, use of cariprazine led to a greater least squares mean change from baseline to week 26 in PANSS-FSNS than did risperidone (−8·90 points for cariprazine *vs* −7·44 for risperidone; least squares mean difference [LSMD] −1·46, 95% CI −2·39 to −0·53; p=0·0022; effect size=0·31). The change from baseline was greater for cariprazine treatment at week 14 until the final follow-up at week 26 (figure 2). For the secondary efficacy parameter, least squares mean change from baseline to endpoint in PSP total score, use of cariprazine led to a greater change than risperidone (14·30 points for cariprazine *vs* 9·66 for risperidone; LSMD 4·63, 2·71 to 6·56; p<0·0001; effect size=0·48). The change from baseline was greater for cariprazine treatment at week 10 until the final follow-up at week 26 (figure 3). Descriptive statistics for mean (SD) baseline and change from baseline scores are shown in the appendix.

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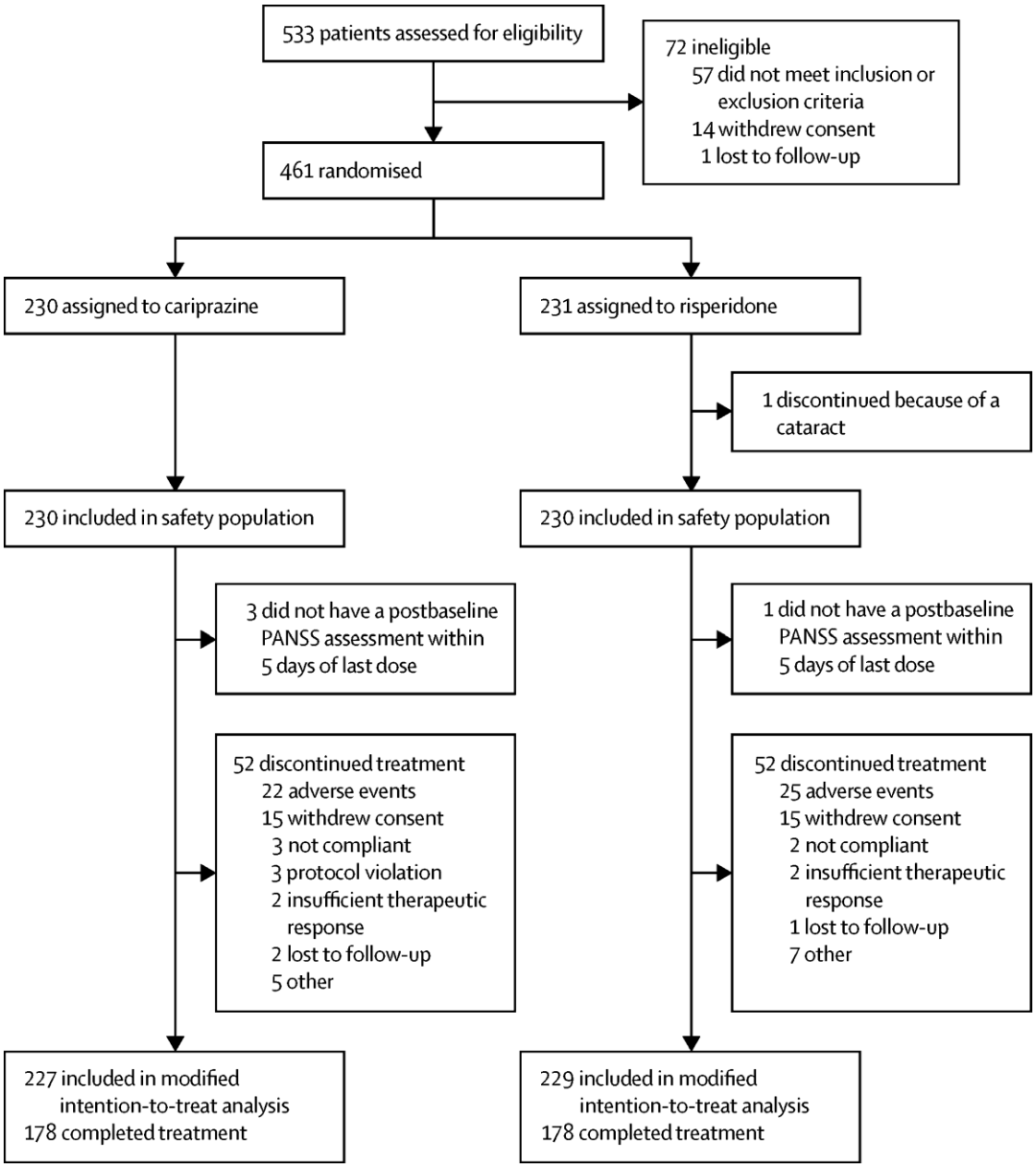

Figure 1: **Trial profile**

For the **study protocol** see https://www.clinicaltrialsregister.eu/ctr-search/search?query=rgh-188-005

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	Cariprazine group (n=230)	Risperidone group (n=230)
Safety population		
Characteristics		
Age (years)		
Mean (SD)	40·2 (10·5)	40·7 (11·2)
Median (IQR)	39·5 (32·0–48·0)	40·0 (31·0–49·0)
Sex		
Men	124 (54%)	140 (61%)
Women	106 (46%)	90 (39%)
Race		
White*	221 (96%)	217 (94%)
Not recorded	9 (4%)	13 (6%)
Bodyweight (kg)	80·14 (16·70)	77·54 (15·17)
BMI (kg/m²)	27·03 (4·90)	26·06 (4·65)
History of schizophrenia		
Time from schizophrenia diagnosis to informed consent (years)	11·98 (8·14)	12·96 (9·17)
Number of acute exacerbations		
<5	148 (64%)	126 (55%)
5–10	61 (27%)	79 (34%)
11–15	11 (5%)	20 (9%)
>15	10 (4%)	5 (2%)
Modified intention-to-treat population†		
Rating scale baselines scores		
PANSS-FSNS score	27·7 (2·6)	27·5 (2·4)
Personal and Social Performance total score	48·8 (10·9)	48·1 (10·7)
PANSS-FSPS score	8·7 (2·7)	8·6 (2·6)
Calgary Depression Scale for Schizophrenia	0·7 (1·2)	0·9 (1·3)
SAS items 1 to 8	0·3 (0·7)	0·3 (0·7)

Data are mean (SD), n (%), or as indicated. PANSS factor score for negative symptoms scoring: 7 to 49 (a higher score indicates worse severity); Personal and Social Performance Scale scoring: 1 to 100 (a higher score indicates better functioning); PANSS factor score for positive symptoms scoring: 5 to 35, a higher score indicates worse severity; Calgary Depression Scale for Schizophrenia scoring: 0 (absent) to 3 (severe); SAS items 1 to 8 scoring: range 0 to 32 (a higher score indicates worse severity). BMI=body-mass index. PANSS-FSNS=Positive and Negative Syndrome Scale factor score for negative symptoms. PANSS-FSPS=Positive and Negative Syndrome Scale factor score for positive symptoms. SAS=Simpson-Angus Scale.

*Data pertaining to ethnic origin was either not collected (at study centres in France) or was recorded as white.

†n=227 for cariprazine group and n=229 for risperidone group.

Table 1: **Baseline characteristics**

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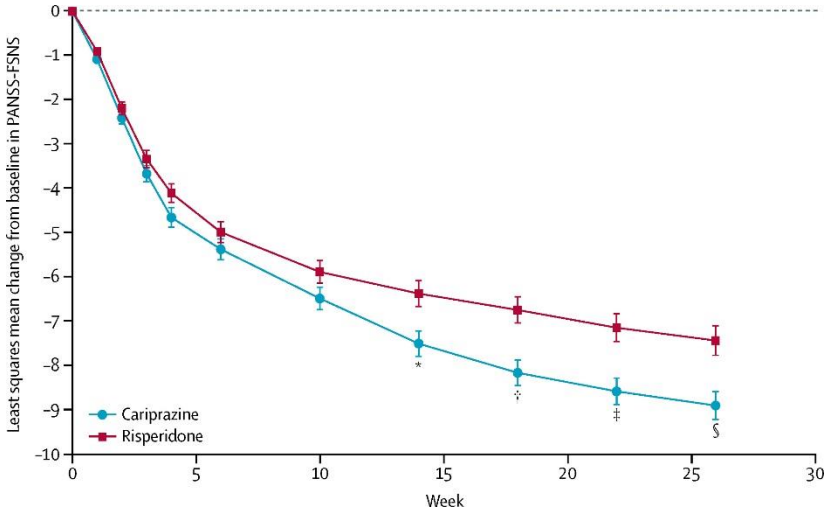

Figure 2: **Mean change from baseline to week 26 in PANSS-factor score for negative symptoms**
p=0·0092 for the overall treatment effect of cariprazine versus risperidone. PANSS-FSNS=Positive and Negative Syndrome Scale factor score for negative symptoms. *p=0·0079. †p=0·0011. ‡p=0·0016. §p=0·0022.

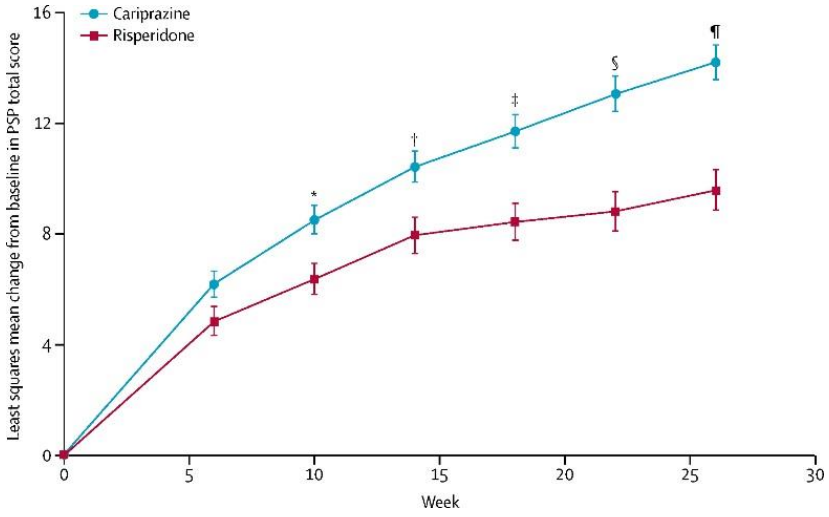

Figure 3: **Mean change from baseline to week 26 in PSP total score**
p<0·0001 for the overall treatment effect of cariprazine versus risperidone. PSP=Personal and Social Performance Scale. *p=0·0053. †p=0·0046. ‡p=0·0004. §p<0·0001. ¶p<0·0001.

Improvements from baseline were also seen in favour of cariprazine treatment for other efficacy parameters (table 2), including CGI-Improvement (CGI-I) and CGI-Severity (CGI-S) scales. Treatment effects between cariprazine and risperidone did not differ for PANSS total score, PANSS positive subscale score, and PANSS general psychopathology score (table 2). We noted greater improvements for patients treated with cariprazine versus those treated with risperidone in the PSP subdomains of self-care, personal and social relationships, and socially useful activities but not in the disturbing and aggressive behaviours area (table 2). Response to treatment (decrease ≥20% in PANSS-FSNS) was achieved by more patients treated with cariprazine by 26 weeks than those treated with risperidone (odds ratio 2·08; p=0·0022); the number needed to treat (NNT) was nine.

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	Cariprazine group (n=227)	Risperidone group (n=229)	LSMD (95% CI)	p value
Additional efficacy (repeated measures ANCOVA mixed effects model)*				
CGI-S score	−0·95 (0·05)	−0·74 (0·05)	−0·21 (−0·36 to −0·06)	0·0052
PANSS				
Total score	−16·90 (0·80)	−14·80 (0·81)	−2·10 (−4·34 to 0·13)	0·065
Negative subscale score	−8·63 (0·32)	−7·16 (0·34)	−1·48 (−2·38 to −0·57)	0·0015
Positive subscale score	−1·40 (0·21)	−1·41 (0·16)	0·01 (−0·52 to 0·54)	0·96
General psychopathology subscale score	−7·14 (0·41)	−6·42 (0·42)	−0·72 (−1·86 to 0·43)	0·22
CGI-I score	2·53 (0·07)	2·89 (0·07)	−0·37 (−0·55 to −0·19)	<0·0001
PSP				
Self-care area score	−0·70 (0·05)	−0·50 (0·05)	−0·20 (−0·34 to −0·06)	0·0044
Socially useful activities area score	−0·95 (0·05)	−0·60 (0·06)	−0·35 (−0·50 to −0·20)	<0·0001
Personal and social relationships area score	−0·85 (0·05)	−0·61 (0·05)	−0·24 (−0·37 to −0·10)	0·0009
Disturbing and aggressive behaviour area score	−0·06 (0·01)	−0·04 (0·02)	−0·02 (−0·07 to 0·02)	0·30
Pseudospecificity measures (repeated measures ANCOVA mixed effects model)*				
PANSS-FSPS	−1·07	−1·08	0·01 (−0·43 to 0·45)	0·96
CDSS total score	−0·28	−0·22	−0·06 (−0·33 to 0·21)	0·66
SAS items 1–8	0·01	0·05	0·05 (−0·21 to 0·12)	0·58
PANSS-FSNS responder rates at week 26 (≥20% decrease in baseline score)†				
Achieved response				
Yes	157 (69%)	133 (58%)	..	..
No	70 (31%)	96 (42%)	..	..

Data are least squares mean change from baseline to week 26 (SE) or number (%). CGI-I scoring: 1 (very much improved) to 7 (very much worse); CGI-S scoring: 1 (normal) to 7 (among the most extremely ill patients); PANSS scoring: 30 to 210 (lower score is favourable); PANSS negative and positive subscale scoring: 7 to 49 (lower score is favourable); PANSS general psychopathology subscale scoring: 16 to 112 (lower score is favourable); PSP area scoring: 1 to 6 (lower score is favourable). PANSS negative subscale consists of items N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (passive or apathetic social withdrawal), N5 (difficulty in abstract thinking), N6 (lack of spontaneity and flow of conversation), and N7 (stereotyped thinking). LSMD=least squares mean difference. CGI-S=Clinical Global Impressions-Severity. PANSS=Positive and Negative Syndrome Scale. CGI-I=Clinical Global Impressions-Improvement. PSP=Personal and Social Performance scale. PANSS-FSPS=PANSS factor score for positive symptoms. CDSS=Calgary Depression Scale for Schizophrenia. SAS=Simpson-Angus Scale. PANSS-FSNS=PANSS factor score for negative symptoms. *Analyses were done on all postbaseline scores measured with only observed cases without imputation of missing values. †Logistic regression model based on Firth's penalised likelihood approach with treatment group, study centre, and baseline value as covariates.

Table 2: **Additional efficacy parameters and pseudospecificity measures**

In the parameters we analysed to assess pseudospecific effects, least squares mean changes from baseline for PANSS-FSPS, CDSS total score, and SAS items 1–8 were small and similar for cariprazine and risperidone (table 2). These results exclude indirect effects related to positive, depressive, or extrapyramidal symptom improvement as a factor in negative symptom improvement.

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The median duration of treatment with cariprazine or risperidone was 182 days (IQR 180·0–182·0). The mean daily dose from baseline to endpoint was 4·2 mg (SD 0·6) for patients treated with cariprazine and 3·8 mg (0·4) for patients treated with risperidone; the modal daily dose (excluding uptitration) was the target dose for 209 (95%) of 221 patients treated with cariprazine and 216 (95%) of 227 patients treated with risperidone.

Adverse events were reported in similar percentages of patients in both treatment groups (table 3). One death occurred during double-blind treatment as a result of two serious adverse events (brain tumour and pulmonary carcinoid tumour) in a patient treated with risperidone; the death was not considered by the investigator to be related to treatment. During double-blind treatment, the only serious adverse event that occurred in more than one patient was schizophrenia (four [2%] patients in each group).

Changes in clinical laboratory values and physical examinations were similar between treatment groups and generally not considered clinically significant (table 4). No clear differences were seen in metabolic parameters or weight change. The number of patients with postbaseline abnormal vital signs reported as treatment-emergent adverse events, including hypertension and orthostatic hypotension, was small in both treatment groups (seven [3%] patients given cariprazine and five [2%] given risperidone). Orthostatic hypotension treatment-emergent adverse events were reported in two (1%) patients given cariprazine and one (<1%) given risperidone. No patients had increases in QT interval from baseline longer than 500 ms measured with either Bazett's formula or Fridericia's formula.

Extrapyramidal symptoms were assessed by treatment-emergent adverse events and rating scale assessments (table 3). Akathisia was the most common treatment-emergent adverse event related to extrapyramidal symptoms. Only one (<1%) patient given risperidone had a severe treatment-emergent adverse event that was related to extrapyramidal symptoms; the remainder of events were considered mild or moderate. Although most treatment-emergent adverse events that were related to extrapyramidal symptoms were considered associated with treatment, these symptoms resulted in study discontinuation for only four (2%) patients given cariprazine and three (1%) given risperidone. Use of rescue medication for extrapyramidal symptoms was low and similar for patients treated with cariprazine or risperidone (no patients were given diphenhydramine; 11 [5%] patients given cariprazine and ten [4%] given risperidone received antiparkinson drugs [eg, trihexyphenidyl hydrochloride, biperiden]; three [1%] patients given cariprazine and three [1%] given risperidone received propranolol hydrochloride).

For ophthalmology parameters, we detected no clinically significant between-group differences in change from baseline to endpoint in visual acuity (appendix). We observed no clinically significant changes in intraocular pressure, and most patients had normal colour vision and physical findings at baseline and week 26 or end of treatment.

Based on the Columbia Suicide Severity Rating Scale assessment, suicidal ideation was reported in one patient given cariprazine at weeks 3 and 10, and in two patients in each treatment group at week 26; suicidal behaviour (suicide attempt) was reported as a serious adverse event that was not considered to be related to treatment in one patient given risperidone. The investigator considered the serious adverse event resolved on the day of the suicide attempt, but the patient was admitted to hospital for aggravation of schizophrenia and withdrawn from the study.

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	Cariprazine group	Risperidone group
Double-blind treatment		
Deaths	0	1/230 (<1%)*
Patients with any SAE	7/230 (3%)	7/230 (3%)
Total number of SAEs reported	7	12
Patients with any AE	123/230 (53%)	131/230 (57%)
Total number of AEs reported	270	317
Safety follow-up		
Deaths	0	0
Patients with any SAE	2/201 (<1%)	0
Total number of SAEs reported	2	0
Patients with any AE	7/201 (3%)	3/205 (1%)
Total number of AEs reported	7	3
Disposition, severity, and association with study drug during the study†		
Patients who discontinued because of an AE‡	23/230 (10%)	27/230 (12%)
Patients who discontinued because of an SAE	5/230 (2%)	7/230 (3%)
Patients with any AE related to study drug	84/230 (37%)	95/230 (41%)
Patients with maximum severity of any AE		
Mild	72/230 (31%)	74/230 (32%)
Moderate	55/230 (24%)	55/230 (24%)
Severe	7/230 (3%)	11/230 (5%)
Common TEAEs during double-blind treatment (affecting ≥3% in either group)		
Insomnia	21/230 (9%)	23/230 (10%)
Akathisia	19/230 (8%)	12/230 (5%)
Schizophrenia§	15/230 (7%)	10/230 (4%)
Headache	13/230 (6%)	24/230 (10%)
Anxiety	13/230 (6%)	11/230 (5%)
Somnolence	9/230 (4%)	13/230 (6%)
Nausea	9/230 (4%)	6/230 (3%)
Fatigue	5/230 (2%)	10/230 (4%)
Dizziness	4/230 (2%)	11/230 (5%)
Cogwheel rigidity	4/230 (2%)	8/230 (3%)
Nasopharyngitis	3/230 (1%)	7/230 (3%)
EPS		
EPS-related TEAEs		
Including akathisia and restlessness	33/230 (14%)	29/230 (13%)
Excluding akathisia and restlessness	9/230 (4%)	14/230 (6%)
Akathisia	19/230 (8%)	12/230 (5%)
Treatment-emergent parkinsonism (SAS score ≤3 at baseline and >3 at any double-blind assessment)	15/230 (7%)	22/230 (10%)
Treatment-emergent akathisia (BARS score ≤2 at baseline and >2 at any double-blind assessment)	27/230 (12%)	21/230 (9%)

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Data are n (%). SAE=serious adverse event. AE=adverse event. TEAE=treatment-emergent adverse event. EPS=extrapyramidal symptom. SAS=Simpson-Angus Scale. BARS=Barnes Akathisia Rating Scale. *One death was reported in a patient in the risperidone group on day 121 (study drug discontinued on day 120), which was a result of pulmonary carcinoid tumour, brain tumour, and mediastinal metastases SAEs that were considered unrelated to study drug. †Includes double-blind treatment period and safety follow-up. ‡One additional patient treated with cariprazine and two additional patients treated with risperidone who were categorised as having an AE that led to discontinuation during the safety evaluation were categorised differently for patient disposition. §MedDRA terms for the preferred AE term schizophrenia include schizophrenia aggravated, schizophrenia exacerbated, and schizophrenia relapse.

Table 3: **Summary of adverse events in the safety population**

	Cariprazine group		Risperidone group	
	n assessed	Value	n assessed	Value
Serum chemistry				
Total cholesterol (mmol/L)	209	−0·14 (0·87)	200	0·01 (0·80)
LDL cholesterol (mmol/L)	209	−0·03 (0·75)	200	0·08 (0·72)
HDL cholesterol (mmol/L)	209	−0·06 (0·23)	200	−0·05 (0·23)
Triglycerides (mmol/L)	208	−0·16 (0·78)	200	−0·04 (0·88)
Fasting glucose (mmol/L)	209	0·15 (1·12)	199	0·23 (1·10)
Creatine kinase (U/L)	209	8·49 (135·69)	200	−13·17 (223·40)
ALT (U/L)	209	−0·39 (19·73)	200	0·71 (17·90)
AST (U/L)	209	0·24 (10·66)	200	0·30 (12·79)
Alkaline phosphatase (U/L)	209	−1·87 (16·35)	200	1·66 (25·40)
Total bilirubin (mmol/L)	209	0·54 (4·91)	200	0·30 (5·79)
Vital signs				
Supine systolic blood pressure (mm Hg)	216	−0·62 (9·57)	215	−0·26 (9·84)
Supine diastolic blood pressure (mm Hg)	216	−0·81 (8·59)	215	−0·03 (7·78)
Supine pulse rate (bpm)	216	−0·82 (10·69)	215	0·94 (10·45)
Bodyweight (kg)	216	−0·36 (3·36)	215	0·64 (3·61)
BMI (kg/m^2)	216	−0·13 (1·19)	215	0·21 (1·26)
Waist circumference (cm)	215	−0·08 (3·98)	215	−0·12 (4·22)

Data are mean change from baseline to week 26 or end of treatment (SD). ALT=alanine aminotransferase. AST=aspartate aminotransferase. BMI=body mass index.

Table 4: **Changes in select laboratory parameters and vital signs in the safety population**

ANCOVA/LOCF and PMM sensitivity analyses confirmed the robustness of the primary MMRM analysis (see appendix). In post-hoc analyses, response to treatment assessed with a more stringent PANSS-FSNS response criterion (decrease ≥30%) was achieved by 113 (50%) of 227 patients given cariprazine and 83 (36%) of 229 patients given risperidone (p=0·0033); the NNT was eight. Additionally, we noted differences in favour of cariprazine compared with risperidone in the number of patients with CGI-I response (p=0·0003), PSP total score change of more than 10 points

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(p=0·0010), and number/proportion of patients who shifted to a higher PSP category (p=0·0010) (appendix).

Discussion

In our study, patients given cariprazine had a greater improvement in predominant negative symptoms of schizophrenia than did patients given risperidone; the difference between treatments seemed to favour cariprazine at every assessment, with statistical significance from week 14. Patients given cariprazine also had a greater improvement in functioning, suggesting that improvement in negative symptoms translated to improved community functioning for these patients. To our knowledge, this trial is the first large-scale study done in patients with schizophrenia and with predominant negative symptoms that has provided evidence of clinically significant improvement for an antipsychotic drug applied as monotherapy; additionally, this study found a significant advantage for one new-generation antipsychotic drug over another.

Additional outcome measures reinforced the robustness of the primary and secondary results. Global improvement in the disease state was shown by improvement for cariprazine over risperidone on the CGI-I and CGI-S. Differences in PANSS total score, positive subscale score, and general psychopathology score were not larger in either group, substantiating that the change in predominant negative symptoms was not a result of improvement in positive or overall symptoms. Increased PANSS-FSNS response rates for cariprazine compared with risperidone supported the clinical significance of other study results. Additionally, pseudospecificity measures supported that improvement of predominant negative symptoms in patients given cariprazine occurred independently of improvement in other symptoms (ie, positive, depressive, extrapyramidal symptoms) known to affect negative symptoms.

Given the considerable unmet medical need in this therapeutic area, it is important to consider that any amount of change could be clinically relevant to patients without other treatment options. In our study, several analyses show that changes for patients with predominant negative symptoms given cariprazine were clinically significant. The effect sizes for cariprazine on the PANSS-FSNS (0·31) and PSP (0·48) are considered clinically significant for antipsychotic treatment compared with placebo; because cariprazine was being compared to an active control with proven antipsychotic efficacy, these effect sizes might suggest even greater clinical relevance. Furthermore, an effect of this size on the PSP, a scale with well established face validity, is a compelling sign of clinical relevance because restored patient functioning is a critical component of recovery. PSP improvement of more than 10 points and shifts to a less severe PSP category additionally show clinically relevant functional improvement for cariprazine.

The NNT for one additional PANSS-FSNS response for cariprazine was nine; an NNT less than ten versus placebo suggests that an intervention has clinical advantages. When the more stringent threshold for response of 30% or more was applied, the difference between treatments remained significant for cariprazine over risperidone, with an NNT of eight. Additionally, a between-treatment difference in rate of response for each criteria investigated was more than 10%, the standard of clinical significance. Collectively, these measures support the expectation that differences for cariprazine over risperidone also represented clinically significant improvement in predominant negative symptoms in patients with schizophrenia.

Negative symptoms contribute to reduced psychosocial functioning and quality of life in patients with schizophrenia. A longitudinal study showed that negative symptoms predicted long-term impairment in global psychosocial functioning, relationships, and work performance.[17] In addition to the clinically significant PSP total score improvement in our study, greater improvement for patients given cariprazine versus risperidone was seen in the PSP subdomains (self-care, personal and social relationships, and socially useful activities) that correspond to the activities of daily living. This improvement could greatly contribute to patient rehabilitation and the ability to

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participate in community mental health programmes. Moreover, higher PSP scores are associated with greater adherence to therapy,[18] suggesting that concurrent improvement in negative symptoms and PSP scores are associated with better adherence to antipsychotic therapy, although the direction of this association cannot be inferred from this study. Differences were not seen in the PSP disturbing and aggressive behaviour areas, which was expected because patients with psychotic symptoms or violent behaviour were excluded from study participation.

Because of the findings that second-generation antipsychotics are mainly effective against the positive symptoms of schizophrenia, the European Medicines Agency (EMA) and the FDA have both endorsed negative symptoms as a specific target for drug development.[19, 20] EMA guidelines state that a claim for negative symptom efficacy should only be made if specially designed studies in patients with predominant negative symptoms are done. As such, the duration of negative symptoms and the onset of a stable episode of schizophrenia should be documented. Specific inclusion and exclusion criteria should be applied to ensure that patients have true negative symptoms, not symptoms related to depressive symptoms or extrapyramidal symptoms. Improvement in negative symptoms should be shown through validated scales and presented as the difference between baseline and endpoint; responder rates should be provided and functional improvement should be shown as the secondary outcome measure.

Few prospective studies of approved antipsychotics have investigated primary negative symptoms in patient populations with well characterised negative symptoms;[21] most published reports are derived from post-hoc analyses of large studies that were not specifically designed to assess patients with predominant negative symptoms. Amisulpride has been widely investigated for predominant negative symptoms, and amisulpride has been indicated for treatment of negative symptoms in patients with schizophrenia in several European countries. Amisulpride has shown efficacy versus placebo in several studies published between 1995 and 1999.[22, 23, 24, 25] In two active-controlled studies published in 2006, in patients selected for predominant negative symptoms, the findings for amisulpride were equivocal. Results of a 6-month trial that compared low-dose and high-dose olanzapine and amisulpride with placebo only found significant improvement for low-dose olanzapine versus placebo.[26] In a 12-week trial comparing amisulpride and ziprasidone treatment, equivalent improvement in negative symptoms and comparable improvement in overall psychopathology and global illness severity were shown.[27] Concomitant improvement in functioning in patients with predominant negative symptoms given amisulpride has not been investigated.[2]

Despite the expectation that improved efficacy in negative symptoms of schizophrenia would be a characteristic trait of second-generation antipsychotics, results of a meta-analysis showed that only four (risperidone, amisulpride, clozapine, and olanzapine) of nine second-generation drugs were more effective than first-generation antipsychotics in treating negative symptoms.[28] The included studies were not done in patients with predominant negative symptoms; however, the authors concluded that efficacy in negative symptoms cannot be considered a central characteristic of atypicality. Additional evidence for second-generation antipsychotic monotherapy for predominant negative symptoms has shown that clozapine does not seem to be effective,[2] and asenapine was not superior to olanzapine in two randomised double-blind trials, although both treatments improved negative symptoms.[29] CGI-I response rates (score of 1 or 2) were 45·9% for asenapine and 54·9% for olanzapine in one of the studies,[29] and 24·4% for asenapine and 27·2% for olanzapine in the other.[29] Additionally, a statistically significant difference on the PANSS negative subscale was noted in favour of olanzapine versus haloperidol in a small randomised controlled study in patients with primary negative symptoms; response rates (20% decrease in PANNS negative subscale score) were 43·7% for olanzapine and 31·6% for haloperidol.[30]

Beyond monotherapy, other drugs are used adjunctively with antipsychotics for predominant negative symptoms in schizophrenia. Antidepressants are a common adjunctive treatment choice

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given the overlap between predominant negative symptoms and depressive symptoms, but supporting evidence is scarce.[21] Drugs with other mechanisms of action (eg, glutamatergic, cholinergic, glycine transport inhibitors) are in development or are being assessed as adjunctive treatment options; to date, clinical trial evidence is modest and limited by heterogeneous patient populations and disparate negative symptom criteria.[2]

In our study, the number of completers was high (77% in each group). The most common adverse events in patients given cariprazine were insomnia, akathisia, schizophrenia, headache, and anxiety. Adverse events related to extrapyramidal symptoms that were considered to be related to treatment occurred in most patients in both groups; however, discontinuations and use of rescue medication for extrapyramidal symptoms were low, suggesting that symptoms related to extrapyramidal symptoms were manageable. The collective assessment of safety parameters suggests that cariprazine was generally well tolerated in this patient population.

A strength of our study is its conduct according to EMA recommended guidelines for studies of negative symptoms, which are closely linked to recommendations put forward by an international panel of experts.[31] While our results are highly applicable to patients with predominant negative symptoms, they might not be generalisable to patients with secondary negative symptoms. Interpretation of results might be limited by the absence of a placebo control; however, randomisation of patients with schizophrenia to placebo for a study of this duration might be ethically problematic and could result in increased risk of relapse. The use of two active-treatment arms could have encouraged some treatment effect in both groups as a result of factors usually attributed to a placebo effect. For example, participation in a clinical trial, knowingly receiving active treatment, frequent study visits, and hope of improvement could have enhanced the treatment effect in both groups. Although the effect of cariprazine was significantly greater than the effect of risperidone, this result does not exclude the possibility that risperidone had a treatment effect of its own, which would be supported by the results of the meta-analysis that found greater efficacy against negative symptoms for risperidone versus first-generation antipsychotics.[28] Effects of previous antipsychotic treatment, which were discontinued 2–4 weeks after baseline, might have contributed to the absence of lasting changes in metabolic parameters or weight changes. As is common practice in clinical trials, the same raters generated ratings on various scales, so the potential for rating crossover cannot be excluded. Finally, we cannot exclude the possibility that some positive effects on predominant negative symptoms might have been a result of factors that were not measured, such as cognitive improvement.

Results from this study indicate that cariprazine treatment was more effective than risperidone in the improvement of predominant negative symptoms in patients with schizophrenia. Because cariprazine was superior to another second-generation antipsychotic in the treatment of predominant negative symptoms, patients who have shown improvement in positive symptoms but continue to have negative symptoms that are disabling while on an antipsychotic other than cariprazine might benefit from cariprazine treatment. These findings suggest that cariprazine has the potential to affect the standard of care and health-care policy decisions for the predominant negative symptoms of patients with schizophrenia, a symptom domain with inadequate treatment options.

Contributors

GN contributed as the sponsor's Chief Medical Officer, supervising all aspects of the trial. IL contributed to trial planning and design, data analysis, data interpretation, post-hoc analyses, and preparation of the manuscript. PC contributed to the design, statistical design, evaluation and interpretation of findings, and preparation of the manuscript. ES contributed as study director to trial planning, clinical project management, data analysis, and preparation of the manuscript. BS contributed to trial design, trial planning, clinical project management, medical monitoring, data analysis and reporting, post-hoc analyses, and preparation of the manuscript. JH contributed to trial planning, clinical project management, medical monitoring, data analysis, and preparation of

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the manuscript. AB contributed to medical monitoring, data analysis, and preparation of the manuscript. MD contributed to the design and the interpretation of post-hoc analyses supporting the design of the study, and contributed to the trial planning, study conduct, medical monitoring, data analysis and interpretation, study report, and review of the manuscript. SD contributed to data interpretation and preparation of the manuscript. IB contributed to trial design, trial planning, data collection, interpretation of the findings, and preparation of the manuscript. SM contributed as a clinical and scientific expert to data interpretation and preparation of the manuscript. WWF contributed to trial design, trial planning, data analysis, and preparation of the manuscript.

Declaration of interests

GN, IL, ES, BS, JH, and AB report personal fees from Gedeon Richter Plc, outside the submitted work. GN and IL have a patent issued for cariprazine. BS has a patent pending for cariprazine. MD reports to have been a Gedeon Richter employee during the preparation, the conduct, and the reporting of the study. SD reports personal fees from Allergan, and other from Allergan, outside the submitted work. IB reports grants and personal fees from Eli Lilly, and personal fees from EGIS, Janssen/Janssen-Cilag, Lundbeck, Medavante, Gedeon Richter, and Servier, outside the submitted work. SM reports personal fees from Allergan, Lundbeck, Takeda, Teva, Otsuka, and Roche, and grants from Forum, outside the submitted work. WWF reports grants and personal fees from Janssen-Cilag, Otsuka, Lundbeck, and Boehringer Ingelheim, and personal fees from Roche, Takeda, Amgen, Teva, Targacept, and Richter, outside the submitted work. PC has no competing interests.

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Supplementary appendix

Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial

Web appendix material:

Methods

Screening

Patients were well known to investigators; a psychiatric history had to be provided to investigators to ensure that patients had predominant, persistent negative symptoms and low levels of positive symptoms. The psychiatric history had to include documentation of the schizophrenia diagnosis for at least 1 year before screening; comorbidities such as depression, EPS, and high levels of positive symptoms that could interfere with the diagnosis and assessment of negative symptoms were considered exclusionary.

Inclusion and exclusion criteria

Stringent inclusion and exclusion criteria were applied (***Table 1***). To evaluate whether improvements in negative symptoms were secondary to improvements in other psychopathological domains (ie, pseudospecific), we assessed changes in positive and depressive symptoms and clinically relevant parkinsonism. As such, patients with a score ≥4 on more than two specific positive PANSS items (delusions, hallucinatory behavior, grandiosity, suspiciousness, or unusual thought content) and patients with moderate to severe depressive symptoms (Calgary Depression Scale for Schizophrenia [CDSS] total score >6) were excluded; additionally, patients with parkinsonism as judged by the investigator and/or a score >3 on the sum of the first eight items of the Simpson-Angus Scale [SAS]) were excluded.

Key inclusion criteria

- Men and women, aged between 18-65 years (inclusive), diagnosed with schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text revision (DSM-IV-TR); all diagnostic subtypes were allowed
- Predominant negative symptoms present for at least 6 months based on medical records and investigator judgment
- Onset of schizophrenia known for at least 2 years
- Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) ≥24
- Score ≥4 on at least 2 of the following PANSS negative items: blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation
- Negative pregnancy test and use of adequate contraception by women of childbearing potential
- Patients being treated with antipsychotic medication at screening were receiving maximum dosage equivalent to risperidone 6 mg/d (patients taking 1 medication) or risperidone 8 mg/d (patients taking the maximum 2 medications)
- Normal physical examination, vital signs, clinical laboratory test results, and electrocardiogram (ECG) results or abnormal results that were judged not clinically significant
- Body mass index (BMI) was between 18 and 40 kg/m2, inclusive

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Key exclusion criteria

- Current DSM-IV-TR–based primary diagnosis of mental retardation or an Axis I disorder other than schizophrenia
- Other psychiatric, neurological, or behavioral disorders that may have interfered with the conduct or interpretation of the study

Unstable patient condition:

- Hospital admission for or history of acute exacerbation of schizophrenia within 6 months of study
- Major increase in psychiatric care or imprisonment within 6 months of study
- PANSS factor score for positive symptoms (PANSS-FSPS) >19
- To avoid potential pseudospecificity: score of ≥ 4 on more than 2 of the following PANSS positive items: delusions, hallucinatory behavior, grandiosity, suspiciousness, unusual thought content
- Treatment with clozapine within 12 months of study, except episodic use at doses≤100 mg/d for the treatment of sleep disorder at all sites other than France
- Presence of moderate to severe depressive symptoms, defined as a Calgary Depression Scale for Schizophrenia (CDSS) total score >6
- Treatment with antidepressant medications within 3 months of study
- Significant risk of suicide within 12 months of study (based on investigator judgment, Columbia-Suicide Severity Rating Scale (C-SSRS) scale information; and/or 1 life-threatening suicide attempt within 5 years of study)
- Violent behavior within 12 months of study (based on investigator judgment and/or PSP scale Disturbing and Aggressive Behaviors subscale scores of "Marked," "Severe," or "Very Severe"
- Treatment with risperidone within 6 weeks of study
- History of nonresponse to an adequate trial of risperidone for a psychotic episode
- Single episode of schizophrenia without residual symptoms (DSM-IV-TR criteria)
- Substance abuse or dependence (other than nicotine or caffeine) within 12 months of study
- History of intolerance or hypersensitivity to cariprazine, risperidone, or designated rescue medications, or any history of severe drug allergy or hypersensitivity
- Clinically relevant parkinsonian symptoms (EPS) (based on investigator judgment and/or sum of the first 8 items on the Simpson Angus Scale (SAS) >3
- Treatment with additional psychotropic medications was prohibited; no rescue medications for rigidity and akinesia were allowed during the prospective lead-in period, and since they could interfere with the evaluation of negative symptoms, the need for continued use was assessed at least once a week
- Concomitant treatment with additional psychotropic medications with the exception of lorazepam (or oxazepam or diazepam in countries where lorazepam was not readily available) for agitation, irritability, hostility, and restlessness; eszopiclone, zopiclone, zolpidem, zolpidem extended release, chloral hydrate, or zaleplon for sleep; diphenhydramine, benztropine or equivalent, or propranolol for EPS
- Any concurrent medical condition that could interfere with the conduct of the study, confound the interpretation of study results, or endanger patient well being

Table 1. **Key inclusion and exclusion criteria**

Additional outcome measures and safety assessments

Additional efficacy measures included the Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) Scales (assessed at all study visits), PANSS Positive and Negative subscales

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(all study visits), PSP functional domain subscales (socially useful activities, personal and social relationships, self-care, disturbing and aggressive behaviors [screening, baseline, weeks 6, 10, 14, 18, 22, and 26 and week 26]), and the PANSS-FSNS responder rate (decrease ≥20% at endpoint) at week 26.

Safety assessments included adverse event (AE) reports (all study visits), clinical laboratory and vital sign parameters (screening, baseline, all weeks 14 and 26), electrocardiogram (ECG) findings (screening, baseline, all weeks 14 and 26), the Columbia-Suicide Severity Rating Scale (C-SSRS) (all study visits), standardized ophthalmology assessments (lead-in visit, week 26), and EPS/movement disorder scales (Barnes Akathisia Rating Scale [BARS], Abnormal Involuntary Movement Scale [AIMS], and SAS [all study visits]).

Statistical methods

Two sensitivity analyses were conducted on the primary and secondary efficacy parameters. The analysis of covariance (ANCOVA) sensitivity analysis used the last observation carried forward (LOCF) approach with the treatment group and study center as factors and the baseline PANSS-FSNS (primary parameter) or PSP score (secondary parameter) as a covariate. The pattern-mixture model (PMM) sensitivity analysis was based on non-future dependent missing value restrictions using the dataset with missing values and a reduced dataset disregarding the early termination data; values for delta were selected as 0 to 10 by increments of 1. Imputation of missing values and analysis were performed multiple times; the inference of the PMM analysis was based on the combined estimates using the standard multiple imputation technique.

Analyses of additional efficacy parameters were performed using an MMRM similar to the one used for the primary analysis; the baseline score for the variable of interest was used as a covariate (the CGI-S was the explanatory variable for the CGI-I). Week 26/ET PANSS-FSNS responder rates were analyzed using a logistic regression model updated to include Firth's penalized likelihood approach in order to achieve model convergence; the model included treatment group, study center, and the baseline value as covariates. Pseudospecificity parameters were analyzed using an MMRM similar to the one used for the primary efficacy parameter.

Safety parameters were reported using descriptive statistics. EPS were evaluated by AE reports and rating scale assessments; treatment-emergent parkinsonism was defined as an SAS score ≤3 at baseline and >3 at any double-blind assessment and treatment-emergent akathisia was defined as a BARS score ≤2 at baseline and >2 at any double-blind assessment.

Results

Efficacy

Descriptive statistics for mean (SD) baseline and change from baseline scores for the primary and secondary efficacy parameters are presented in ***Table 2***.

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Efficacy Measure		Cariprazine group n=227		Risperidone group n=229	
		n[1]	Mean (SD)	n[1]	Mean (SD)
PANSS-FSNS	Baseline score	227	27·7 (2·57)	229	27·5 (2·39)
	Observed case				
	Week 26 score	175	18·5 (4·74)	178	19·6 (5·05)
	Change from baseline to week 26	175	-9·3 (4·72)	178	-7·9 (5·30)
	LOCF				
	Week 26 score	227	19·5 (5·04)	229	20·5 (5·27)
	Change from baseline to week 26	227	-8·2 (4·99)	229	-6·9 (5·34)
Personal and Social Performance total score	Baseline score	227	48·8 (10·85)	229	48·1 (10·72)
	Observed case				
	Week 26 score	175	64·0 (10·82)	178	59·7 (13·70)
	Change from baseline to week 26	175	15·1 (10·94)	178	11·5 (10·89)
	LOCF				
	Week 26 score	218	61·4 (12·44)	225	57·2 (14·46)
	Change from baseline to week 26	218	12·6 (11·53)	225	9·1 (11·39)

n[1]= number of patients with assessment at indicated time point. On the PANSS-FSNS, a higher score indicates worse severity; on the Personal and Social Performance scale, a higher score indicates better functioning.
PANSS-FSNS= Positive and Negative Syndrome Scale factor score for negative symptoms.

Table 2. **Summary statistics for primary and secondary efficacy measures (mITT population)**

Sensitivity analyses

In the ANCOVA/LOCF analysis, the LSMD in CFB to endpoint was statistically significant for cariprazine over risperidone on both the PANSS-FSNS (-1·32 [-2·19, -0·46]; p=0·003) and PSP total score (3·66 [1·71, 5·60]; p<0·001). Additionally, PMM sensitivity analyses confirmed the primary MMRM analysis for CFB to endpoint in PANSS-FSNS and PSP total score with statistically significant results for cariprazine over risperidone on all delta values when using the dataset with missing values and on a reduced dataset disregarding early termination data.

Safety

Visual acuity

No clinically significant differences were detected in change from baseline to Week 26/end of treatment in visual acuity between the treatment groups (***Table 3***).

Parameter		Cariprazine group n=230		Risperidone group n=230	
		n[1]	Mean (SD)	n[1]	Mean (SD)
Best-corrected visual acuity right eye	Baseline score	199	0·1 (0·3)	191	0·2 (1·5)
	Week 26 score	199	0·1 (0·3)	191	0·1 (0·3)
	Change from baseline to week 26	199	-0·0 (0·2)	191	-0·1 (1·5)
Best-corrected visual acuity right eye	Baseline score	199	0·1 (0·3)	191	0·2 (1·5)
	Week 26 score	199	0·1 (0·3)	191	0·1 (0·3)
	Change from baseline to week 26	199	-0·0 (0·1)	191	-0·1 (1·5)

n[1]= number of patients with assessment at indicated time point.

Table 3. **Summary statistics for change from baseline in best-corrected visual acuity at week 26 or early termination (safety population)**

Post hoc analyses

In post hoc analyses (***Table 4***), response to treatment using a more stringent PANSS-FSNS response criterion (decrease ≥30%) was achieved by significantly more cariprazine- than risperidone-treated patients. Additionally, statistically significant differences in favor of cariprazine over risperidone were also seen in the number of patients with CGI-I response, PSP total score change >10 points, and patients who shifted to a higher PSP category.

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Post hoc analyses		Cariprazine group n=227	Risperidone group n=229	p value versus risperidone
PSP improvement at week 26				
PSP >10 point improvement, n (%)	Yes, n (%)	126 (57·8)	96 (42·7)	—
	No, n (%)	92 (42·2)	129 (57·3)	—
Cariprazine versus risperidone		Odds ratio (95% CI)		—
		2.1170 (1.35, 3.31)		0·0010
PSP shift to a higher category at week 26, n (%)	Yes, n (%)	150 (68·8)	125 (55·6)	—
	No, n (%)	68 (31·2)	100 (44·4)	—
Cariprazine versus risperidone		Odds ratio (95% CI)		—
		2·17 (1·37, 3·44)		0·00095
PANSS-FSNS responder rates at week 26 (≥30% decrease in baseline score)				
Achieved response, n (%)	Yes, n (%)	113 (49·8)	83 (36·2)	—
	No, n (%)	114 (50·2)	146 (63·8)	—
Cariprazine versus risperidone		Odds ratio (95% CI)		—
		1·97 (1·25, 3·09)		0·0033
CGI improvement at week 26				
CGI-I response (score 1 [“very much”] or 2 [“much”] improved	Yes, n (%)	110 (48·5)	78 (34·1)	—
	No, n (%)	117 (51·5)	151 (65·9)	—
Cariprazine versus risperidone		Odds ratio (95% CI)		—
		2·37 (1·48, 3·77)		0.0003
CGI-S improvement (≥1 point improvement)	Yes, n (%)	143 (63·0)	126 (55·0)	—
	No, n (%)	84 (37·0)	103 (45·0)	—
Cariprazine versus risperidone		Odds ratio (95% CI)		—
		1·64 (1·03, 2·60)		0·036

CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; ITT=intention to treat; PANSS-FSNS=Positive and Negative Syndrome Scale factor score for negative symptoms; PSP=Personal and Social Performance scale.

***Table 4*. Post hoc analyses (mITT population)**