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THE ROLE OF THE DOPAMINERGIC SYSTEM IN NEGATIVE SYMPTOMS OF SCHIZOPHRENIA – AN INDUSTRY OUTLOOK INTO THE DEVELOPMENT OF A NEW-GENERATION ANTIPSYCHOTIC

PhD thesis

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LIST OF ABBREVIATIONS

5-HT_{2A}: serotonin 2A receptor

AIMS: Abnormal Involuntary Movement Scale

ANCOVA: analysis of covariance

BARS: Barnes Akathisia Rating Scale

CAINS: Clinical Assessment Interview for Negative Symptoms

CAR: cariprazine

CDSS: Calgary Depression Scale for Schizophrenia

CfB: Change from baseline

CGI-I: Global Clinical Impression – Improvement

CGI-S: Global Clinical Impression – Severity

C-SSRS: Columbia-Suicide Severity Rating Scale

DAT: dopamine transporter

DSM: Diagnostic and Statistical Manual of Mental Disorders

EMA: European Medicines Agency

EOS: early onset schizophrenia

EPS: Extrapyramidal symptoms

ET: early termination

FDA: Food and Drug Administration

ICF: informed consent form

IMP: investigational medicinal product

ITT: intent-to-treat

LOCF: lost observed data carried forward

LS = least squares

LSMD = least squares mean difference

MedDRA: Medical Dictionary for Regulatory Activities

MMRM: mixed-effects model for repeated measures

MoA: mechanism of action

NSA-16: Negative Symptom Assessment

PANSS: Positive and Negative Symptom Scale

PANSS-FSNS: PANSS factor score for negative symptoms

PANSS-FSPS: PANSS factor score for positive symptoms

PSP: Personal and Social Performance Scale

RCT: randomized clinical trial

SANS: Scale for the Assessment of Negative Symptoms

SAS: Simpson-Angus Scale

SCID-CT: Structured Clinical Interview for DSM-IV – Clinical Trials Version

SE: standard error

TEAE: treatment-emergent adverse event

VMAT2: vesicular monoamine transporter type 2

1. INTRODUCTION

1.1. Epidemiology and symptomatology of schizophrenia

Schizophrenia is lifelong mental disorder that is listed among one of the most disabling illnesses according to the World Health Organization. (1) Schizophrenia is a global condition, with a median lifetime prevalence of 0.749% and an incidence rate is about 1.631 per 100 000 people. (2,3) Typically, schizophrenia begins in adolescence/early adulthood, with the most common age of onset is between 18 and 25 for men and between 25 and 35 for women. (4)

Although in most cases the onset is between the age of 18 and 35, there are still cases of schizophrenia manifesting before the age of 18 (early onset schizophrenia – EOS) or after the age of 40 (late onset schizophrenia). While the prevalence of EOS is usually estimated around 0.5%, some publications suggest a higher (1/3 of patients having their first psychotic episode before the age of 19) or lower prevalence (1:500-10 000 in mid-adolescence). (5–11)

Men are diagnosed with schizophrenia slightly more often than women (1.4:1), however, there is a shift between the male-to-female ratio with age: there are more males in the younger while more females in the older age groups. (3,12) This might be attributed to the lower age of onset and diagnosis and also to the fact the males tend to be more affected by substance use disorder and tobacco use resulting in higher mortality rates. (3)

There are various classification systems used in psychiatry. The most widely used and accepted system is the Diagnostic and Statistical Manual of Mental Disorders (DSM) that has been developed by the American Psychiatric Association. The latest version of the DSM is called DSM-5 Text Revision, published in 2022. (13) The original DSM-5 was introduced in 2013, replacing the previous version, DSM-IV Text Revision. (14,15) One of the major changes of the DSM-5 compared to DSM-IV was to exclude the subtypes of schizophrenia. (16)

Although the DSM-IV was replaced by the DSM-5 more than 10 years ago, the studies discussed in this research had been initiated before its introduction, therefore the DSM-IV Text Revision nomenclature and classification will be applied throughout this thesis.

Schizophrenia is a complex syndrome, described generally by symptoms categorized into 3 domains: positive, negative and cognitive symptoms. (17)

Positive symptoms describe behaviors that are additional and not present in normal behavior and are the most disturbing and prominent for the society. These symptoms include hallucinations, delusions, disorganized thoughts and behaviors. (15,18)

The most common form of hallucination in schizophrenia is auditory (voices, or other sounds with high impact on the patient's overall mental state), while visual and somatic ones are less common. (15,18)

Delusions are also common symptoms of schizophrenia, manifesting in false believes. There are many ways to categorize delusions. (19) One of the most common distinctions are whether the delusions are bizarre (implausible) or non-bizarre (plausible). Further examples for delusion types are persecutory, referential, grandiose, erotomanic, nihilistic, and somatic. (15,18)

Disorganization can be either behavioral or in thinking. While disorganized behavior can be observed easily (e.g. bizarre or inappropriate actions, gestures), disorganized thoughts can sometime only be diagnosed with a more in-depth interview with the patient. Disorganized thoughts can manifest in inappropriate, off-topic answers to simple questions, abrupt switching of topics, creation of non-existing words, meaningless sentences.

Negative symptoms on the other hand are less obvious and disturbing for society, however, has a higher impact on the patients' and caregivers' burden. (20) These symptoms represent absence or reduction in behaviors that are present in people without a mental disease. Although the diagnosis of schizophrenia can only be done after the first positive symptoms occur, in most cases negative symptoms are already present in the prodromal phase of schizophrenia. (15) These symptoms include: alogia, blunted affect, avolition, apathy, anhedonia and asociality. (21)

Cognitive symptoms usually also manifest before the first acute episode of schizophrenia as negative symptoms. In general, patients with schizophrenia show some kind of impairment in cognition, especially in the following areas: working memory, attention, visual or verbal learning/memory, processing speed. (22–24)

The course of the disease can vary from individual to individual. (25) In the prodromal phase of the disease, negative symptoms and cognitive impairment may already be present. (26) When the patient experiences the first acute exacerbation, positive symptoms become the most prominent symptoms, and they remain the leading burden for the patient in the early stages of the disease. Medical treatment with antipsychotics is initiated at the first acute phase of schizophrenia. Due to the treatment and the natural course of the disease, the psychotic (positive) symptoms fade away and the more persistent negative symptoms become prominent. However, the pattern of acute exacerbations and states of remissions show a considerable variation among patients. The usual course of the disease is visualized on **Figure *1***. (27)

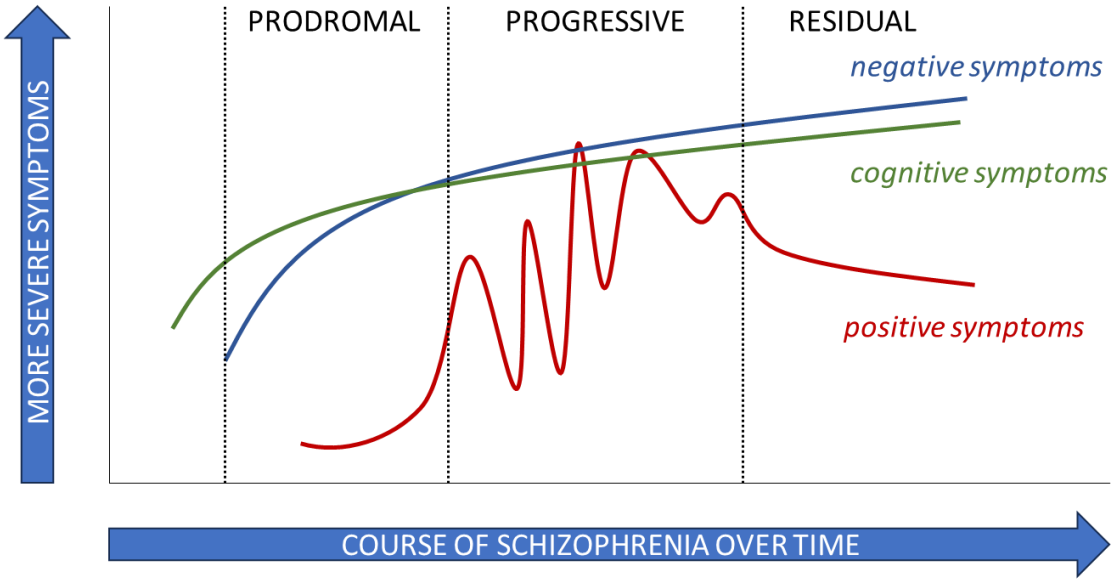


Figure 1 – Typical course of disease progression in schizophrenia

1.2. The role of the dopaminergic system in schizophrenia and broader neuropsychiatry

Although the pathology of schizophrenia is unknown, the most widely accepted theory is the dopamine hypothesis. (28) This theory has been the basis of antipsychotic medications for the last 70 years.

There are 5 major dopamine receptors, which can be further categorized into 2 groups: the D1-like and the D2-like receptors. While the D1-like receptors (D1 and D5) stimulate, the D2-like receptors (D2, D3, D4) on the other hand inhibit neurotransmitter release, resulting in a GO and a STOP signal, respectively. (29,30)

There are four major dopamine pathways in the brain: the nigrostriatal, the mesolimbic, the mesocortical and the tuberoinfundibular. (31) All of these dopamine pathways are important to understand the pathology of schizophrenia, as well as the mechanism of action (MoA)/unwanted side-effects of current antipsychotic mediation.

Psychosis is thought to be caused by the hyperactivity of the D2 receptors in the mesolimbic pathway. However, this pathway also plays a role in emotion and pleasure. Stimulating this pathway with stimulants or cocaine can cause similar effects on the long-term as schizophrenia. Blocking this pathway is the basis of all currently available antipsychotic's effectiveness on positive symptoms. (4)

The nigrostriatal pathway on the other hand is responsible for the most important and disturbing side-effects of antipsychotic mediation. The degeneration of this pathway is the cause of Parkinson's disease, therefore, artificial blockage of the pathway by antipsychotics causes similar movement disorders as Parkinson's disease: extrapyramidal symptoms (EPS), akathisia, tardive dyskinesia. (4)

Another important pathway that affects the side-effect profile of an antipsychotic is the tuberoinfundibular. Normally, dopamine is inhibiting the release of prolactin through this pathway, which is downregulated in post-partum women to initiate lactation. D2-blocking agents have a similar effect, causing unwanted hyperprolactinemia in both sexes. (4)

The last pathway, the mesocortical, is the most interesting and still the exact role in the pathology of schizophrenia and other mental disorders remains unclear. There are several theories that dopamine deficiency on this pathway is responsible for the cognitive and negative symptoms. Therefore, an antipsychotic agent that blocks this dopamine pathway would further worsen such symptoms. (4)

The dopaminergic system plays an important role in other diseases as well. (32)

One classical example is the drug, levodopa, in Parkinson's disease. Levopdopa treats the motor symptoms of the disease, however, due to its MoA also increases the risk of drug induced psychosis. (33) Another example of a viable drug target is the synaptic dopamine reuptake process through the presynaptic dopamine transporter (DAT) and then the intracellular vesicular monoamine transporter type 2 (VMAT2). Stimulant drugs like methylphenidate inhibit the DAT, increasing the synaptic dopamine concentration which

has a positive effect in the treatment of attention deficit hyperactivity disorder, while the inhibition of VMAT2 (valbenazine) is used for the treatment of tardive dyskinesia and chorea associated with Huntington's disease. (34,35)

1.3. Antipsychotic medications

Currently available antipsychotic medications all share a common MoA: they target the dopaminergic pathways. (36) However, there are differences between the different generations of antipsychotics, which are called first-generation ("typical"), second-generation ("atypical") and third-generation ("atypical partial agonists") (***Table 1***). (37)

Table 1 – Classification of antipsychotic medication

Typical APs	**Atypical APs**			
	5-HT$_{2A}$ & D$_2$ antagonists			***D$_2$ partial agonists***
haloperidol	*risperidone*	*ziprasidone*	*asenapine*	*aripiprazole*
chlorpromazine	*olanzapine*	*clozapine*	*iloperidone*	*brexpiprazole*
perphenazine	*quetiapine*	*paliperidone*	*lurasidone*	*cariprazine*

The first antipsychotic used in psychosis associated with schizophrenia was chlorpromazine in the 1950s. This was the first drug within its class called "typical antipsychotic". (37) Although the exact MoA is unknown, it is thought to act as a pure D2-receptor antagonist, resulting in decrease of positive symptoms, however, causing the "typical" side-effect of EPS through the blockage of the nigrostriatal pathway, as well as hyperprolactinemia through the tuberoinfundibular pathway. (4) Although the effectiveness of these "typical antipsychotics" were satisfactory, they only addressed positive symptoms with notable EPS-like side-effects.

Second-generation, "atypical" antipsychotics were designed to address the undesirable EPS effects while maintaining good control over the positive symptoms. (31) The theory

behind this aim was to add a second main target apart from D2 antagonism for these drugs: blocking the serotonin 2A receptors (5-HT_{2A}). 5-HT_{2A} receptors ae present presynaptically in the nigrostriatal pathway and they regulate dopamine release. The presence of serotonin inhibits dopamine release, thus by blocking the 5-HT_{2A} receptors, dopamine release will increase, resulting in reduced motor side effects. (38) On the other hand, serotonin has little to no effect on the mesolimbic pathway, maintaining the efficacy of D2 receptor antagonism on positive symptoms. (31)

Third-generation "partial agonist" antipsychotics wanted to address not only the positive symptoms and manageable safety profile, but also target other symptoms of schizophrenia, like negative and cognitive symptoms. Apart from partial agonism on the D2 receptors, these drugs also have a unique receptor profile, some targeting other dopamine receptors, like D1 and D3. There is a fine balance how well these new generation drugs bind to D2, D1, D3 receptors and how these compare to the natural binding affinity of dopamine itself. (39–41)

While the role of D1 receptors is uncertain, their high concentration in the prefrontal cortex suggests that D1 receptors might have an effect on cognition, mood and negative symptoms, although the exact mechanism is unknow. Animal models suggest that too much or too little dopamine acting on the D1 receptors of the prefrontal cortex can cause cognitive dysfunction. (36)

The presence of D3 receptors in the brain is more complex. They can either be post- or presynaptic. If post-synaptic, they inhibit the subsequent messenger system, while if presynaptic, they have a major role in regulating (inhibiting) dopamine release. (30) The main areas where D3 receptors are present post-synaptic are the hypothalamus and the ventral tegmental area/substantia nigra, hence it is thought that they have a role in cognition, motivation and mood, making D3 receptors ideal targets for improving cognition, negative symptoms and mood disorders. (42) However, D3 receptors can also be presynaptic in the prefrontal cortex where the main post-synaptic receptor is D1. (30) While a dopamine antagonist might block the D1 receptors, a presynaptic D3 preferring compound can counteract this affect, providing the right balance between inhibition and facilitation, resulting in improvement of the mood, negative and cognitive symptoms. (31)

It is important to mention that D3 receptors, as presynaptic autoreceptors, have a high affinity towards endogenous dopamine, even higher than D2 receptors' affinity. For this reason, even if a compound has a higher selectivity towards D3 than D2, it is unlikely that their affinity is higher than dopamine's, resulting in minimal effect on these brain areas. The only exception is cariprazine which has almost a 10-times higher affinity towards D3 receptors compared to D2 receptors, which was also proved to ensure an in vivo receptor occupancy in humans. (43)

1.4. Cariprazine – a novel D3/D2 partial agonist

Cariprazine is a third-generation antipsychotic, showing partial agonist activity on D3/D2 receptors. Additionally, cariprazine also has a high affinity towards 5-HT_{2B} and 5-HT_{1A} receptors and moderate affinity towards 5-HT_{2A} and H1 receptors (***Figure 2***). (40)

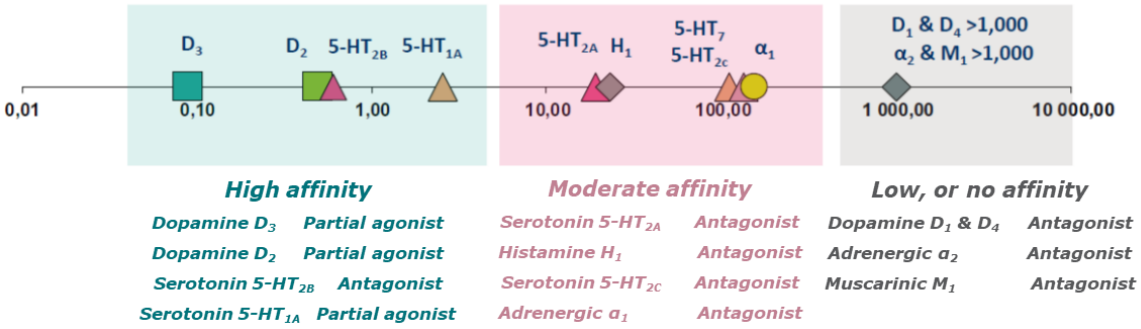


Figure 2 – Receptor affinity of cariprazine

This receptor profile makes cariprazine an ideal candidate to potentially address symptoms beyond psychosis, like negative, cognitive and mood symptoms, while maintaining a beneficial side-effects profile like other atypical antipsychotics.

Cariprazine was developed by Gedeon Richter together with Forest Laboratories (which was acquired by Allergan and then by Abbvie; for simplicity, Abbvie will be used as a development partner in this thesis which refers to these legal entities) and is currently approved for the treatment of schizophrenia in adult patients within the EU and for adult patients for the treatment of schizophrenia, the acute treatment of manic or mixed episodes associated with bipolar I disorder, treatment of depressive episodes associated with bipolar I disorder (bipolar depression), and as adjunctive therapy to antidepressants for the treatment of major depressive disorder in the US. (44,45)

1.5. Cariprazine's efficacy and safety in schizophrenia

The European Medicines Agency (EMA) *Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia* provides a good framework what kind of trials are needed in each development stage to be able to apply for a marketing authorization within the EU region. (46)

According to this guideline, double-blind, randomized, parallel group confirmatory trials are needed to demonstrate the efficacy of an antipsychotic. (46) The late-stage development of drug candidates consists of the Phase II and Phase III clinical trials. (47) Phase II can further be divided into Phase IIa and Phase IIb trials. Both of these trials are called exploratory, however, while the main goal of Phase IIa is to prove early efficacy in the patient population, the aim of Phase IIb trials are more to provide sufficient information for the subsequent Phase III (confirmatory) trials in terms of dosing regimen, appropriate patient (sub)population, safety profile, and endpoints. The Phase III confirmatory studies are the basis of the marketing authorization; therefore, they have to be representative and relevant for the indication and patient population proposed for marketing authorization.

Although, regarding Phase II studies the guideline is less restrictive, it is sensible to mimic the Phase III trial set-up, while keeping the original aims of the trials (e.g. various dose arms for dose finding, more endpoints for signal detection).

In general, the Phase III studies should include a test arm (fixed or flexible dose), and a placebo arm to prove the test drug's superiority over placebo. However, especially in studies in psychiatric disorders the placebo response can be high, therefore, a third type of arm is recommended by the guidelines: an active comparator. The aim of this arm is to show assay sensitivity, meaning that if this arm proves to be superior to placebo, the clinical trial can be considered adequate to assess efficacy. Furthermore, the selected active comparator should have a similar pharmacological profile as the test drug to demonstrate the relative effectiveness of the test compound compared to a drug with already proven efficacy. (46)

Traditionally the primary aim of antipsychotics is to treat the positive symptoms of schizophrenia. As patients showing excessive positive symptoms are more suitable to

demonstrate response to pharmacologic treatment, these trials are conducted in the acute phase of the disease, meaning they enroll patients with an ongoing psychotic episode.

Enrolled patients must have a diagnosis of schizophrenia based on a verified tool, e.g. the SCID-CT (Structured Clinical Interview for DSM-IV – Clinical Trials Version). (46)

The duration of these studies should be sufficiently long to prove maximum efficacy in the acute exacerbation, achieving clinical stability in the patient's symptomatology. Due to the dynamics of the response to antipsychotic treatment in acute exacerbation, a 6-week study duration is sufficient to prove efficacy of the drug candidate compared to placebo. (46)

The primary endpoint of such trials must be a validated test measure which also provides the possibility to assess the new compound's effectiveness compared to other already approved antipsychotics. The Positive and Negative Symptom Scale (PANSS) is the gold standard primary outcome measure in schizophrenia studies. Further endpoints are also important to assess the patient's overall health status. For this, the Clinical Global Impression (CGI) scales are widely used. (46)

In terms of safety, there are some specific aspects that need to be considered due to the nature of the disease, as well as the antipsychotic's mechanism of action.

One of the main concerns of treatments acting on the dopaminergic system are the extrapyramidal side effects. These should be carefully assessed through validated rating scales, like the Barnes Akathisia Rating Scale (BARS), the Simpson-Angus Scale (SAS) and the Abnormal Involuntary Movement Scale (AIMS). Other potential side-effects like hyperprolactinemia, suicidality, metabolic, hematologic, and cardiovascular effects should also be closely monitored throughout the development program. (46)

The cariprazine clinical development in acute setting (short-term efficacy) consisted of two Phase II clinical trials (RGH-MD-03, RGH-MD-16), and there were two Phase III confirmatory trials (RGH-MD-04, RGH-MD-05). The overall study structure was identical throughout these 4 studies as shown in ***Figure 3*** below. (48–51)

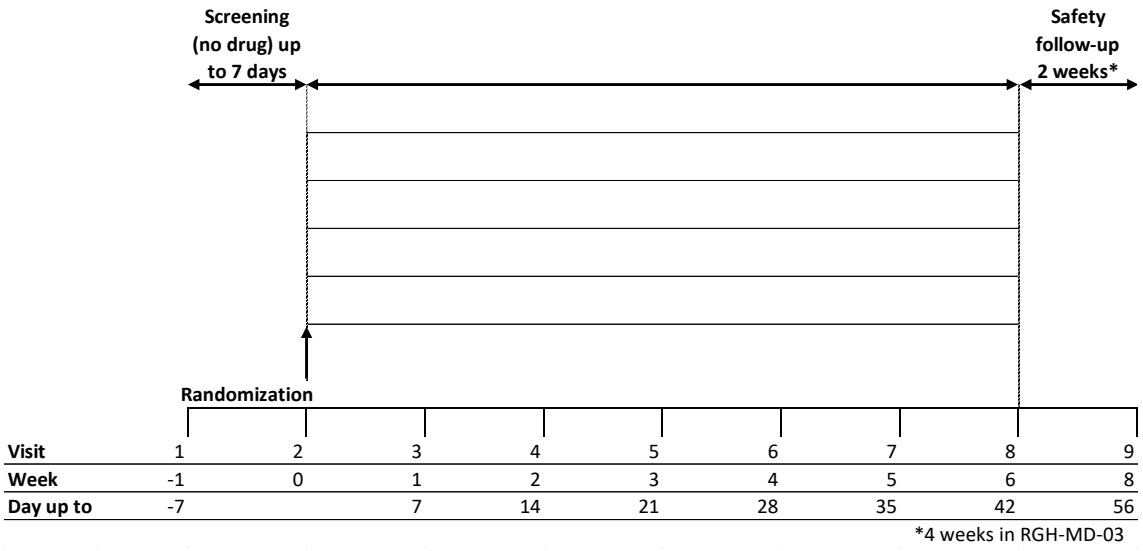


Figure 3 – Overall study design of the acute short-term schizophrenia trials

To assess the efficacy of the study treatments, a no drug washout period was introduced at the beginning of each study. The length of the washout period was based on the half-life of the previous antipsychotic medication the patient had been taking but the duration could no longer than 7 days to prevent substantial worsening of the patient's symptomatology. (48–51)

If the patient met all eligibility criteria at the both the screening (Visit 1) and baseline (Visit 2) visits, they were randomized randomly to the treatment arms. Patients continued to receive a daily regimen of investigational medicinal product (IMP) for the subsequent 6 weeks with a visit at the end of each week. After 6 weeks of treatment, patients discontinued taking the IMP and then were followed-up for another 2 weeks to monitor potential ongoing adverse events. (48–51)

There were differences in the number of treatment arms, the dosing schemes, and dosing regimens in the Phase II/III trials. (48–51)

Table 2 contains the treatment arms and patient disposition data by study.

Table 2 – Summary of treatment arms and patient disposition in the Phase II/Phase III short-term trials

	Exploratory Phase II studies							
	RGH-MD-03			RGH-MD-16				
	Placebo	*Cariprazine 1.5-4.5 mg*	*Cariprazine 6-12 mg*	*Placebo*	*Cariprazine 1.5 mg*	*Cariprazine 3 mg*	*Cariprazine 4.5 mg*	*Risperidone 4 mg*
Screened	521			1011				
Randomized	130	128	134	151	145	147	148	141
Safety population	129	127	133	151	145	146	147	140
ITT population	**126**	**122**	**129**	**148**	**140**	**140**	**145**	**138**
Completed the study	69	68	72	79	90	96	98	101
Withdrawn from the study	60	59	61	72	55	50	49	39

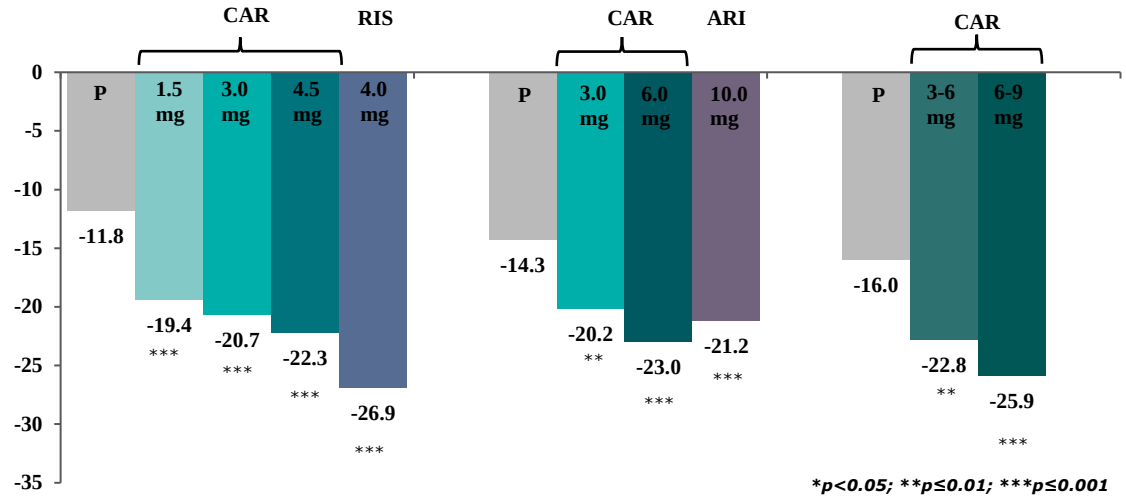
	Confirmatory Phase III studies						
	RGH-MD-04				RGH-MD-05		
	Placebo	*Cariprazine 3 mg*	*Cariprazine 6 mg*	*Aripiprazole 10 mg*	*Placebo*	*Cariprazine 3-6 mg*	*Cariprazine 6-9 mg*
Screened	834				664		
Randomized	153	155	157	152	147	151	148
Safety population	153	155	157	152	147	151	148
ITT population	**149**	**151**	**154**	**150**	**145**	**147**	**147**
Completed the study	95	104	97	114	88	96	86
Withdrawn from the study	58	51	60	38	59	55	62

IIT: intent-to-treat

The *Randomized Population* consisted of all patients in the Screened Population who were randomized to a treatment group. The *Safety Population* consisted of all patients in the Randomized Population who took at least one dose of double-blind investigational product. The *Intent-to-Treat (ITT) Population* consisted of all patients in the Safety Population who had at least one postbaseline assessment on the primary efficacy parameter, the PANSS total score. A patient was considered as a *Completer* if they completed Visit 8, the last visit in the double-blind treatment period. (48–51)

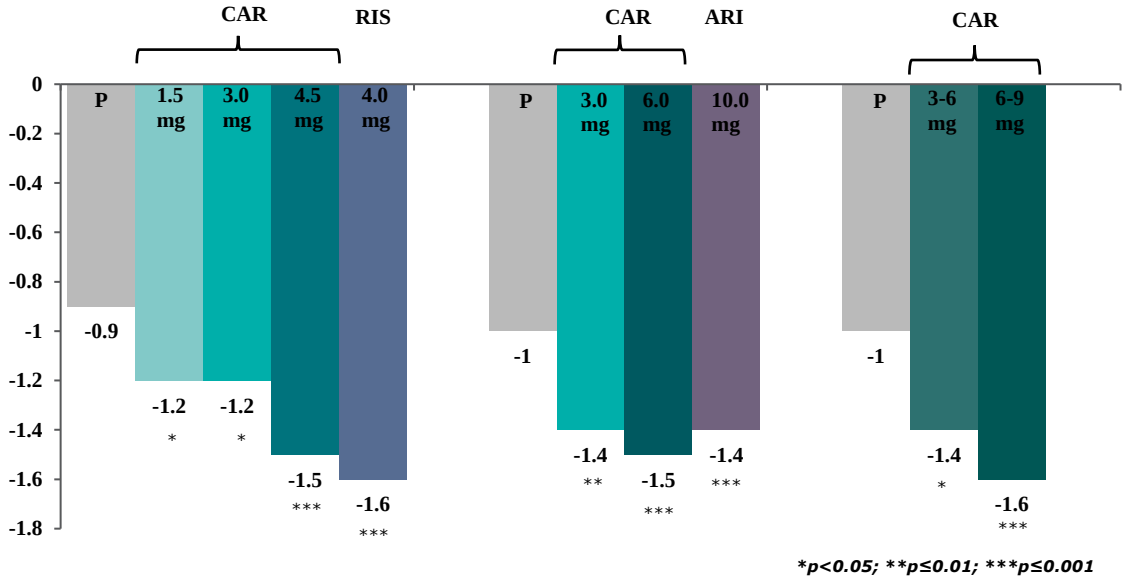
The change from baseline (Visit 2) to Week 6 (Visit 8) on the PANSS total score was used as the primary efficacy parameter. The secondary efficacy parameter was the change from baseline to Week 6 in the Clinical Global Impression – Severity (CGI-S) score. (48–51)

Results on the primary and secondary efficacy endpoints are summarized on ***Figure 4*** and ***Figure 5***.



CAR: cariprazine; RIS: risperidone; ARI: aripiprazole

Figure 4 – Change from Baseline on the PANSS total score in the short-term efficacy trials



CAR: cariprazine; RIS: risperidone; ARI: aripiprazole

Figure 5 – Change from Baseline on the CGI-S score in the short-term efficacy trials

RGH-MD-16, RGH-MD-04 and RGH-MD-05 studies provided sufficient evidence to support the effectiveness of cariprazine on the positive symptoms of schizophrenia. (48–51) Compared to two antipsychotics (risperidone and aripiprazole) with well-established efficacy and similar mechanism of action, cariprazine proved to be as effective as current

gold standard drugs. The Phase IIb and Phase III studies also demonstrated a dose-effect relationship throughout the dose range of 1.5-9 mg daily.

Regarding safety, in the short-term efficacy trials the number of patients experiencing at least 1 treatment-emergent adverse event (TEAE) during the trial was comparable throughout the treatment arms. The highest rate of patients experiencing an adverse event leading to discontinuation was in the placebo group (12.2%); on the active arms these ranged between 9.2% and 10.8% (excluding the dose range on 9-12 mg cariprazine daily). The most common adverse events were (at least 5% of patients and twice the rate of placebo) were extrapyramidal symptoms (including the terms: bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, Parkinsonism, salivary hypersecretion and tremor), somnolence (including the terms: somnolence, sedation and hypersomnia), akathisia, hypertension (including the terms: blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased and hypertension), dizziness and weight increased. (52) Cariprazine was also associated with minimal effects on prolactin levels. (53)

In summary, the short-term efficacy trials proved that cariprazine is effective and well-tolerated in the acute exacerbation of schizophrenia in the adult population. (48–51) The generated evidence confirmed the hypothesis that D2 partial agonism can provide a right balance between the effectiveness in psychotic symptoms and the frequency of dopamine related adverse events.

As part of the regulatory requirements towards the EMA, additionally to efficacy in the acute setting, long-term efficacy also needed to be demonstrated to grant marketing approval. In accordance with the EMA guidance, RGH-MD-06 study investigated the efficacy of cariprazine in preventing relapse in individuals with schizophrenia. (54) The study was a randomized, double-blind, placebo-controlled trial with a total duration of up to 97 weeks. 200 patients who had their schizophrenia symptoms stabilized with cariprazine during the first 20-week open-label treatment phase were then randomized to receive either cariprazine (3, 6, or 9 mg/d) or a placebo for up to 72 weeks. The primary outcome measure was time to relapse, which was defined as a worsening of symptom scores, psychiatric hospitalization, aggressive or violent behavior, or suicidal risk. The

results showed that cariprazine was significantly more effective than placebo in preventing relapse. The time to relapse was significantly longer in the cariprazine group, with only 24.8% of cariprazine-treated patients experiencing a relapse compared to 47.5% on the placebo arm. These findings suggest that cariprazine is a valuable treatment option for relapse prevention in schizophrenia.

Based on the aforementioned studies, the foundation was established to seek European approval for the treatment of schizophrenia in the adult population. However, neither of these studies were able to provide a major differentiation point compared to other antipsychotics.

1.6. Negative symptoms – methodological questions

As detailed in Section 1.5, cariprazine was effective in terms of positive symptoms, that is the basis of approvability of an antipsychotic. However, additional symptoms that are as important and even more burdensome for the patient and their environment as the acute exacerbations. Both negative and cognitive symptoms are adding to the overall disease burden, and in contrary to the positive symptoms, these features worsen throughout the course of the disease and prevail at the residual stage. (27) Based on large-scale randomized trial comparing first- and second-generation antipsychotics, prominent negative symptoms have the greatest impact on patients' quality of life, including probability of finishing high-school, low social and economic functioning, and the ability to live independently. (55)

When the cariprazine Phase III schizophrenia program concluded, there was only one antipsychotic – amisulpride – on the market with the indication of treating predominant negative symptoms of schizophrenia in only limited number of European countries. However, the clinical studies conducted with amisulpride had methodological limitations. (56–59) All of these studies were placebo-controlled studies, two of them with a treatment duration of 6 weeks, and small patient numbers.

Furthermore, a meta-analysis comparing the first- and second-generation antipsychotics proved that although four of the second-generation (amisulpride, olanzapine, risperidone, and clozapine) were more efficacious in both positive and negative symptoms compared

to first-generation antipsychotics, there were no clear differences seen among these second-generation antipsychotics in terms of negative symptoms. (60)

Therefore, negative symptoms still remained a high unmet medical need in patients with schizophrenia, which was also recognized by the main regulatory bodies, like the US Food and Drug Administration (FDA) and the EMA. (61)

One of the biggest challenges in drug developments targeting negative symptoms is the selection of appropriate tools to assess efficacy.

The Positive and Negative Syndrome Scale (PANSS) is a clinical tool used to measure the severity of symptoms in individuals with schizophrenia. It is divided into 3 subscales evaluating positive, negative, and general symptoms of schizophrenia. The PANSS is a 30-item questionnaire, with each item rated on a scale from 1 to 7, based on a structured interview and observations. The PANSS is widely regarded as a gold standard for assessing the effectiveness of antipsychotic treatments. (62)

While the PANSS is the most widely used scale for the overall effectiveness in schizophrenia, the original scale has limitations when it comes to the negative symptoms.

On one hand, the PANSS negative subscale does not measure the motivational or hedonic impairments, on the other hand it contains items (deficit in abstract thinking, stereotyped thinking, and poor attention) that are not related to negative symptoms, but to cognitive impairment. (63,64) There are many other tools developed and used in randomized clinical trials (RCT), like the Negative Symptom Assessment (NSA-16), Scale for the Assessment of Negative Symptoms (SANS), or the Clinical Assessment Interview for Negative Symptoms (CAINS). (65–67) However, these scales have only been used in limited number of RCTs, therefore, regulatory bodies still prefer to see data generated on the PANSS. This also ensures the possibility to assess the relevance of the newly created data compared to historical findings.

Due to the above-described limitations of the original PANSS negative symptoms subscale, there have been various alternations in the PANSS item classifications to better capture the positive, negative and cognitive symptomatology. Although the original PANSS only consisted of 3 dimensions (positive, negative, and the general psychopathology subscales), subsequent analyses suggested that the symptomatology is

more complex, and there are further clusters where the individual PANSS items correlate with each other. The most wide-spread and accepted factor capturing negative symptoms was developed by Marder et al. (68) Factors defined by Marder were: negative, positive, disorganized thought, uncontrolled hostility/excitement, anxiety depression.

The PANSS factor score for negative symptoms (PANSS-FSNS) consists of the following PANSS items:

- N1: blunted affect
- N2: emotional withdrawal
- N3: poor rapport
- N4: passive social withdrawal
- N6: lack of spontaneity
- G7: motor retardation
- G16: active social avoidance.

Applying factor scores instead of the subscales has been validated in various clinical trials assessing negative symptoms and endorsed by the regulatory authorities. During a workshop organized by the International Society of for CNS Clinical Trials and Methodology in 2009 and 2010, representatives from the industry, academia and the major regulatory agencies (FDA and EMA) discussed the shortcomings of current methodologies related to clinical trials in negative symptoms. (61) One of the major discussion points was to define the appropriate assessment tool to capture efficacy in negative symptoms of schizophrenia. The question of a co-primary endpoint assessing functionality had also been discussed but both the EMA and the FDA agreed that a sufficient improvement on negative symptoms on a validated tool is sufficient for a labelled indication. The experts confirmed that SANS, NSA-16 and PANSS are all considered as reliable and validated assessment tools to measure changes in negative symptoms, however, there was a consensus in the panel that the PANSS subscale is not adequate to assess negative symptomatology, and the factor scores are preferred.

The Marder PANSS-FSNS items were also confirmed by another factor analysis by Mohr et al. (69) Although the negative factor consisted of the same items, Mohr defined slightly

different items for the following factors: positive, cognitive impairment, hostility and mood.

Mohr intended to reduce the number dimensions defining the various disease states of schizophrenia, so he proposed that mood disorders and hostility/aggression should not be considered as major factor defining the states but rather cofactors. With this approach, 8 disease states were specified based on the positive, negative, and cognitive symptoms. The level of impairment on all dimensions were also defined by the average individual PANSS score item scores: positive ranging from low (<2.7) – moderate (2.7-3.9) – high (>3.9), negative ranging from low (<2.1) – moderate (2.1-3.4) – high (>3.4) and cognitive low (0-2.9) – high (>2.9). This provided an excellent framework to identify patients with various disease states, including patient with predominant negative symptoms, i.e. high negative symptoms and low to moderate positive symptoms with specific cut-offs on the given PANSS factor scores.

Apart from the PANSS-FSNS, the PANSS positive factor score (PANSS-FSPS) is relevant when defining predominant negative symptoms. It consists of the following items:

- P1: delusions
- P3: hallucinatory behavior
- P5: grandiosity
- P6: suspiciousness/persecution
- G9: unusual thought content.

1.7. Cariprazine and the negative symptoms of schizophrenia – a post-hoc analyses from the short-term studies

As stated before, cariprazine has a higher affinity towards D3 receptors than D2 receptors which in theory could be beneficial in the treatment of negative symptoms (see Section 1.3).

Therefore, although not ideal in trials enrolling patients in their acute phase, post-hoc analyses were performed for potential signals whether cariprazine is effective in negative symptoms as well.

A pooled post-hoc analyses was performed with the two active-controlled acute trials (RGH-MD-16 and RGH-MD-04). (70) First, a subset of patients had to be identified who showed mild to moderate positive symptoms and severe negative symptoms. The tools that were used to identify this subpopulation was the specific PANSS-FSNS and the PANSS-FSPS detailed in Section 1.6. (69) These tools were also applied to assess the improvement on these dimensions of symptomatology.

Altogether, between 20-30% of patients of the ITT population (same definition was applied as for the studies) were eligible for the post-hoc analysis. The baseline characteristics are summarized in **Table *3***.

Table 3 – Baseline characteristics of patient subpopulation eligible for the post-hoc analysis

	Placebo (N=79)	**Cariprazine 1.5-3 mg/day (N=94)**	**Cariprazine 4.5-6 mg/day (N=66)**	**Risperidone 4 mg/day (N=34)**	**Aripiprazole 10mg/day (N=44)**
Completed the study, n (%)	49 (62.0)	71 (75.5)	47 (71.2)	26 (76.5)	34 (77.3)
Age, mean (SD), y	39.3 (11.3)	37.6 (10.9)	37.5 (11.2)	35.6 (10.7)	39.1 (10.4)
Men, n (%)	46 (58.2)	58 (61.7)	41 (62.1)	24 (70.6)	30 (68.2)
PANSS total at baseline, mean (SD)	98.0 (8.1	99.0 (8.9	98.6 (8.5)	99.6 (8.1)	96.9 (7.9)
PANSS -FSNS at baseline, mean (SD)	27.4 (2.8)	27.7 (3.4)	27.7 (3.0)	27.6 (3.6)	27.9 (3.1)
PANSS-FSPS at baseline, mean (SD)	16.6 (2.1)	16.9 (2.0)	16.9 (2.0)	17.2 (1.8)	16.5 (1.6)

n = number of patients in the given category; N = number of patients in the ITT population; SD = standard deviation

The baseline PANSS-FSNS and PANSS-FSPS were similar for all treatment groups.

The applied statistical method used a mixed-effects model for repeated measures (MMRM) approach with treatment group, study, region, visit, region-by-visit interaction, and treatment group-by-visit interaction as fixed effects and baseline value and baseline-by-visit interaction as covariates; p-values represented the test of no difference between the different cariprazine dose groups versus placebo or the comparator treatment arms.

Change from baseline to Week 6 on the PANSS-FSNS showed statistically significant improvement versus placebo in the cariprazine 1.5-3 mg/day (LSMD [95% CI] = -2.0 [-3.6, −0.3], P = 0.0179), the cariprazine 4.5-6 mg/day (LSMD [95% CI] = -3.4 [-5.2, -1.7], P = 0.0002), and the risperidone 4mg/day (LSMD [95% CI] = -2.8 [-5.0, -0.5], P = 0.0149), however, was not statistically significant in the aripiprazole 10 mg/day group (LSMD [95% CI] = -1.0 [-3.0, 1.0], P = 0.3265). Furthermore, the cariprazine 4.5-6 mg/day treatment arm was statistically significantly superior compared to the aripiprazole arm at week 6 (LSMD [95% CI] = -2.4 [-4.5, -0.4], P = 0.0197); **Figure *6***.

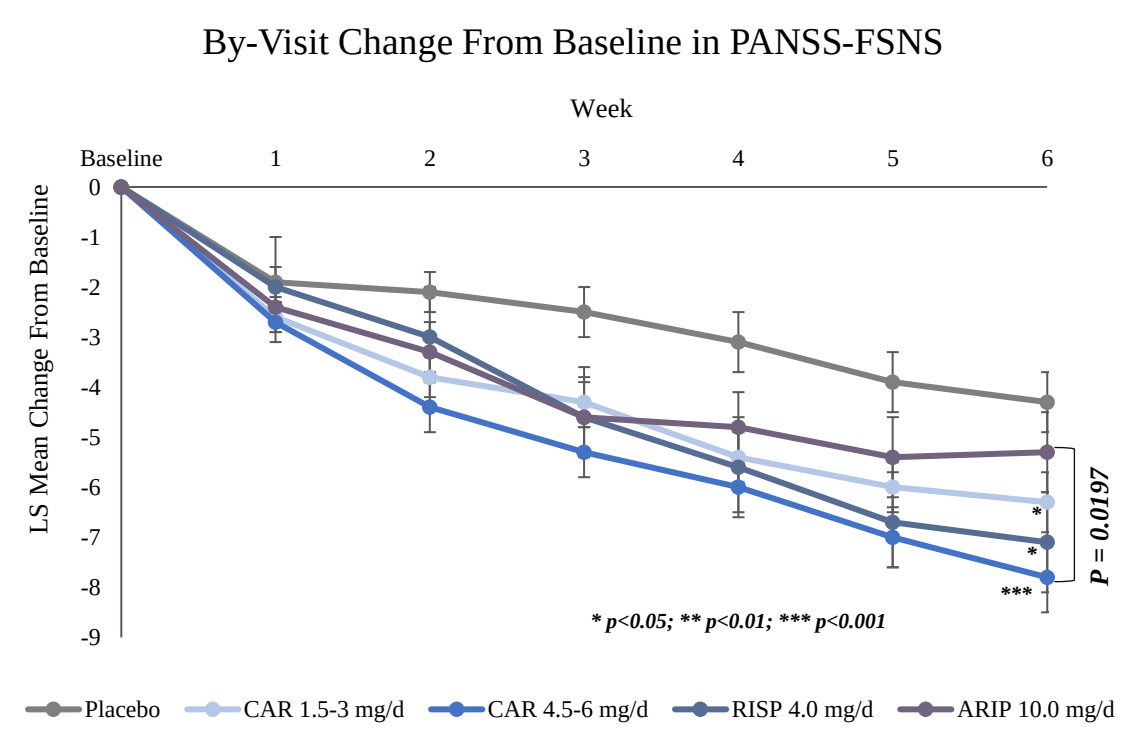


Figure 6 – Change from baseline to Week 6 on the PANSS-FSNS in the pooled acute active-controlled trials in patients with predominant negative symptoms

When we looked at the responders in terms of negative symptoms defined as ≥20% reduction in PANSS-FSNS compared to baseline, only the cariprazine groups were statistically significantly better than placebo (cariprazine 1.5-3 mg/d: -1.4 [-2.7, -0.1], P = 0.0322; cariprazine 4.5-6 mg/d: -2.1 [-3.5, -0.7], P = 0.0038), the risperidone and aripiprazole arms were not (-1.1 [-2.8, 0.7], P = 0.2204; -0.2 [-1.8, 1.3], P = 0.7635, respectively).

The limitations of this post-hoc analysis was the suboptimal length of the study to assess meaningful improvements in this symptom area, as well as the low patient numbers in the active comparator arms.

Based on the promising results of these post hoc analyses, there was a need to verify results in a well-designed prospective study.

2. OBJECTIVES

The objective of this research was to **assess the effectiveness** of a novel D3 preferring D3/D2 partial agonist, cariprazine, on the negative symptoms of schizophrenia.

Based on our post-hoc analysis there was a signal that cariprazine is effective in treating the negative symptoms of schizophrenia.

My objective was to validate or refute the hypothesis of cariprazine's efficacy through a well-designed clinical trial, in details:

- to identify the most suitable endpoint to assess efficacy on the primary negative symptoms of schizophrenia;
- to define the appropriate inclusion and exclusion criteria that ensure a patient population who is suffering from both primary and predominant negative symptoms;
- to define the appropriate efficacy and safety analyses from a medical perspective;
- to evaluate the results and define key messages for the clinical study report.

3. METHODS

A randomized, double-blind, active-controlled Phase IIIb study was initiated to specifically assess the efficacy of cariprazine in patients with predominant negative symptoms of schizophrenia (EudraCT 2012-005485-36). (71)

The study was conducted in 11 European countries (Bulgaria, Croatia, Czech Republic, France, Hungary, Poland, Romania, Russia, Serbia, Spain and Ukraine) between May 2013 and November 2014.

3.1. Overall Study Design

This clinical study was a multinational, randomized, double-blind, active-controlled, parallel-group, fixed/flexible-dose, efficacy and safety study in adult patients with a primary diagnosis of schizophrenia.

The study had 3 periods:

- 4-week prospective lead-in period
- 26-week double-blind treatment period including a 2-week up-titration (Part 1) and a 24-week treatment continuation (Part 2)
- 2-week safety follow-up period

An overall study schematic is shown in ***Figure 7***.

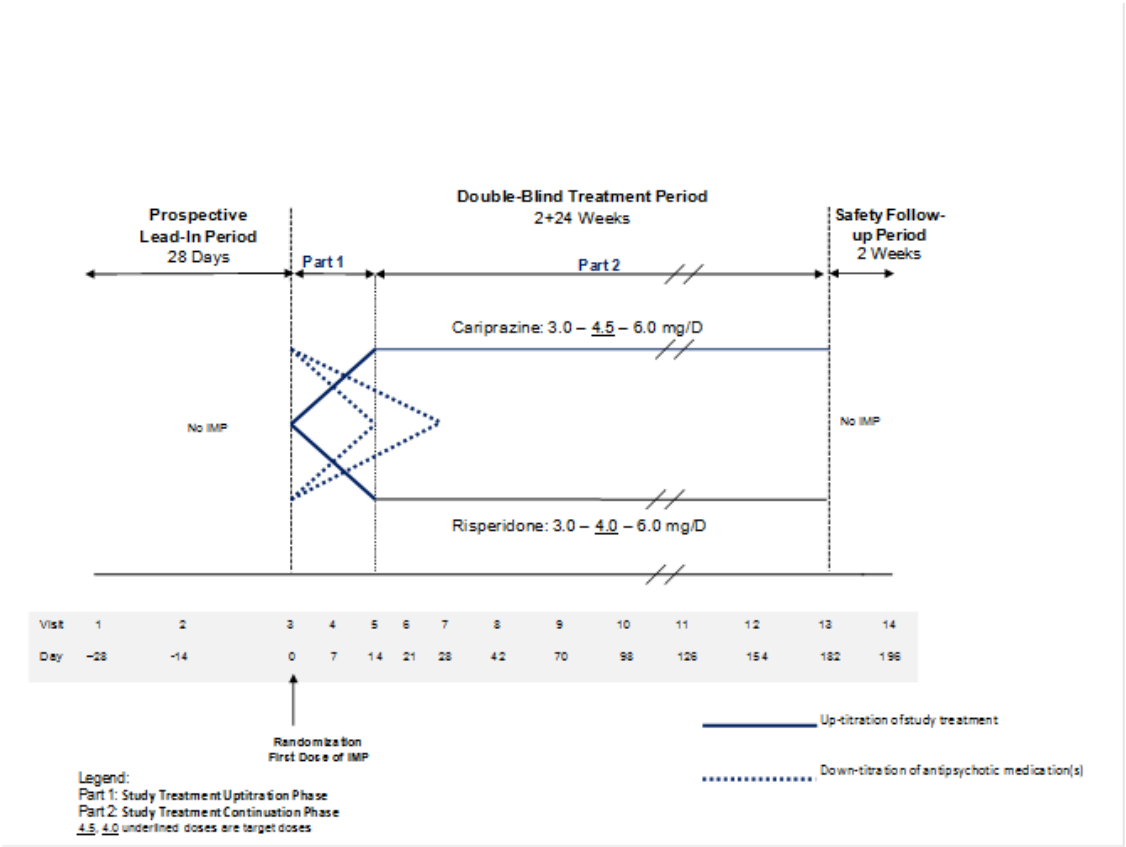


Figure 7 – Overall Study Design – RGH-188-005

After a detailed screening visit (Visit 1) assessing all the inclusion and exclusion criteria (see Section 3.2), if the patient had been deemed eligible for the study, they entered a prospective lead-in period of 4 weeks. At the middle of this period an intermediate visit (Visit 2) took place to assess if the patient had still been eligible (most importantly in terms of their symptom stability). After 4 weeks, the baseline visit (Visit 3) took place where most of the screening criteria were reassessed, and decision was made if the patient had been eligible for randomization. If eligible, patients were randomized in a double-blind way to either cariprazine or risperidone (1:1). The down-titration of their current antipsychotic treatment had to be initiated (based on the investigator's decision, this could have been prolonged up to 4 weeks). During the first week, patients received either 1.5 mg/day cariprazine or 2.0 mg/day risperidone. On the second week, both the cariprazine and risperidone arms were increased to 3.0 mg/day. From the beginning of week 3 patients received their target dose of 4.5 mg cariprazine daily or 4 mg risperidone daily.

Visits had been scheduled weekly during the first month of the double-blind treatment period (Visits 4-7), then the next visit was in 2 weeks (Visit 8). From Visit 9 through Visit 13 the visit interval was 4 weeks.

Investigators were advised to keep the target dose of 4.5 mg/day cariprazine and 4.0 mg/day risperidone as much as possible. However, due to the duration of the study, from Visit 6 onwards investigators had the chance to increase the doses to 6 mg/day in case of impending psychotic relapse, or to decrease to 3 mg/day in case of tolerability. Investigators were encouraged to return to the target dose as soon as the condition of the patient was stabilized. This flexibility was only allowed once in each direction during the double-blind treatment period for each patient.

3.2. Patient Selection

Eligible patients were between the age of 18-65 years, had a diagnosis of schizophrenia based on the DSM-IV-TR by a structured clinical interview (SCID-CT), with an onset of at least 2 years prior to trial screening.

Before any study procedures (including screening activities), patients must have signed an informed consent form (ICF). Patients had to understand the content of the patient information sheet prior signing the ICF.

Patients had to be known directly by the investigator or through referral with available, reliable, and detailed documentation on the patient's history for at least 1 year prior to the screening visit.

Definition of predominance of negative symptoms were defined according to the Mohr methodology: high level of negative symptoms and low to moderate positive symptoms. The same factor scores were applied as for the post-hoc analyses detailed in Section 1.7, the PANSS-FSNS and the PANSS-FSPS. (68,69) Patients had to have predominant negative symptoms for at least 6 months prior to screening based on the medical history available for the investigator.

Patients had to show predominant negative symptoms at the screening and randomization visits based on the following criteria:

- PANSS-FSNS ≥24 and

- a score of ≥ 4 on a minimum 2 of the 3 PANSS items
    - N1 – Blunted affect
    - N4 – Passive/apathetic social withdrawal
    - N6 – Lack of spontaneity and flow of conversation

Patients also had to be stable in their positive symptomatology for at least 6 months prior to screening (i.e. no hospital admission for, or history of acute exacerbation of schizophrenia or major increase in psychiatric care or imprisonment) and had to fulfill the following criteria at screening and at randomization:

- PANSS-FSPS >19 and
- a score of ≥ 4 on more than 2 of the following PANSS items
    - P1 – delusions
    - P3 – hallucinatory behavior
    - P5 – grandiosity
    - P6 – suspiciousness
    - G9 – unusual thought content

Only limited fluctuation of negative and positive symptoms were allowed during the screening period (PANSS-FSNS difference between screening and randomization <25%, PANSS-FSPS increase between screening and randomization <25%).

Patients had to receive at least 1 (maximum of 6 mg/day risperidone equivalent) but maximum 2 (maximum of 8 mg/day risperidone equivalent) antipsychotic that was stable for at least 30 days prior to screening. Treatment with risperidone within 6 weeks prior to screening or history of non-response to an adequate risperidone treatment was exclusionary as well. Additionally, the treatment with clozapine within the last 12 months was forbidden as clozapine is the standard choice of antipsychotic for treatment-resistant schizophrenia.

Patients with moderate to severe depressive symptoms defined as >6 total score on the Calgary Depression Scale for Schizophrenia (CDSS) were also excluded, as well as patients with significant risk of suicide within 12 months prior screening based on all available sources, including those collected on the Columbia-Suicide Severity Rating

Scale (C-SSRS), or who had more than 1 life-threatening suicide attempt in the prior 5 years. (72,73)

Cluster B personality disorders (borderline, antisocial, histrionic, and narcissistic personality disorders), violent behavior and substance abuse or dependence within 12 months of screening were also exclusionary.

Patients were also not eligible who showed clinically significant parkinsonian symptoms as judged by the Investigator or as evaluated by the sum of the first 8 items on the SAS >3.

If patients required concomitant treatment with psychostimulants, sedative/hypnotics/anxiolytics, antidepressants and mood stabilizers, dopamine-releasing drugs or dopamine agonists, psychotropic drugs not otherwise specified (including herbal products), these treatments had to be discontinued immediately or until Visit 2. The only exceptions were the current antipsychotic treatment until the end of the down-titration period, as well as the following:

- 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 (e.g. trihexyphenidyl), or propranolol for EPS.

3.3. Study Variables

All of the below listed scales had to be administered by experienced and certified raters. Experience was assessed based on a questionnaire. There was also a predefined certification procedure for each scale before a physician was allowed to be part of the study as a rater. This procedure consisted of live or online trainings. The ensure consistency among raters, they were asked to apply these scales on example cases. Thereafter these were assessed by a specific group of experts before granting the certification scale by scale for each rater.

Structured Clinical Interview of the Positive and Negative Syndrome Scale

The Structured Clinical Interview (SCI)-PANSS was the primary applied tool in the study to assess the positive symptoms, negative symptoms, and general psychopathology specifically associated with schizophrenia. (62) The scale consists of 30 items, each item can be rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe), therefore the PANSS total score ranges from 30 to 210. The PANSS positive subscale score and the PANSS negative subscale score each contain 7 of the 30 items, and their scores range from 7 to 49. The PANSS general psychopathology subscale score includes 16 of the 30 PANSS items, and ranges between 16 to 112. The primary endpoint was the PANSS-FSNS, which also contains 7 items, with a total score raging between 7 to 49.

Personal and Social Performance Scale

The PSP is a clinician-rated scale assessing the patient's overall functionality with a maximum score of 100. (74) The total score is derived from the following 4 domains: social useful activities, personal and social relationships, self-care, disturbing and aggressive behaviors. The higher the total score shows better patient functioning.

Clinical Global Impression Scales, Improvement and Severity

There are two types of Global Clinical Impression scale: one assessing the severity (CGI-S) and one the improvement (CGI-I). (75) The CGI-S is used by the clinician to record the global severity of the patient's condition at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-I on the other hand shows how much the patient's overall condition has improved or worsened compared to the baseline. The score ranges from 1 (very much improved) to 7 (very much worse).

Calgary Depression Scale for Schizophrenia

The CDSS is a 9-item scale developed specifically to assess the depressive symptoms associated with schizophrenia. (72) All 9 items can range from 0 = absent, 1 = mild, 2 = moderate to 3 = severe.

3.4. Study Outcomes

The primary efficacy parameter of the study was the change from baseline (CfB) to week 26 (Visit 13) on the PANSS-FSNS.

The secondary efficacy parameter was the CfB to week 26 (Visit 13) on the Personal and Social Performance Scale (PSP) total score.

Additional efficacy assessments were the following:

- CfB in PANSS negative subscale score at week 26
- CfB on CGI-S at week 26
- CfB in PANSS total score at week 26
- CfB in PANSS general psychopathology subscale score at week 26
- CGI-I score at week 26
- Responder rate based on the number of patients who achieved a decrease ≥20% compared to baseline in their PANSS-FSNS.

Pseudospecificity was also assessed on the following scales:

- CfB in PANSS-FSPS at week 26
- CfB in CDSS total score at week 26.

The role of pseudospecificity will be discussed in Section 5.2.

Safety was assessed using standard adverse event collection, vital signs, clinical laboratory, body weight, ECG parameters, physical examination, C-SSRS, and the EPS scales (AIMS, BARS, SAS).

3.5. Statistical Methods

The following study populations were defined and used for the statistical analyses:

- Screened population: consisted of all patients who attended screening (Visit 1), signed the ICF, and were assigned a patient number. This population was used to show patient disposition.
- Randomized population: consisted of all patients in the screened population who received a randomization number at the baseline (Visit 3). This population was also used to show patient disposition.
- Safety population: consisted of all patients within the randomized population who at least took one dose of double-blind treatment. This population was used for all safety analyses.

- ITT population: consisted of all patients within the safety population who had at least 1 post-baseline PANSS-FSNS assessment.

There was no per-protocol population defined for this study.

All efficacy analyses were performed on the ITT population, where the baseline was the value captured on the baseline visit (Visit 3) before the first dose of double-blind IMP (or the last available value). All statistical hypothesis tests were performed at the two-sided 5% significance level.

The sample size of 210 per arm was based on a 90% power to detect an effect size of 0.25 at a 2-sided significance level of 5%, with the assumption of a 2.25-point difference between the cariprazine and the risperidone arms, and a 10% drop-out.

The primary analysis was performed using the mixed-effects model for repeated measures (MMRM). Treatment group, study center, visit and treatment-group-by-visit interaction were used as fixed effects and the baseline value and the baseline value-by-visit interaction as covariates. Only observed postbasline scores were used for the analysis, missing values were not imputed.

Sensitivity analyses using the pattern-mixture model and the analysis of covariance (ANCOVA) model with the LOCF approach (with treatment group and center as factors, and baseline PANSS-FSNS as covariate) were also performed to test validity of the primary analysis.

For the secondary endpoint (PSP), the additional efficacy endpoints, and pseudospecificity the same statistical method was used as for the primary parameter (incl. sensitivity analysis for the secondary endpoint). The responder rate analyses were performed with a logistic regression model with treatment group, study center, and the baseline score as covariates.

For the safety endpoints, descriptive statistics were used without statistical hypothesis testing.

4. RESULTS

4.1. Patient Disposition, Demographics and Schizophrenia History

Altogether 533 patients were screened for the study (screened population). 461 were found eligible and were randomized (randomized population), 460 patients received at least one dose of double-blind IMP (safety population), out of which 456 were included in the ITT population. 356 patients (77.4% overall and also in both treatment groups) completed the double-blind treatment period (from baseline to Week 26) and 355 the safety follow-up period as well.

The 104 patients (22.6%) who early terminated (ET) during the double-blind phase, the most common reason for drop-out was due to adverse events (9.6% in the cariprazine and 10.9% in the risperidone groups).

The majority of patients were recruited in Ukraine (118; 25.8%) and Russia (108; 23.5%). 188 patients (40.9%) were recruited from the EU countries (32 patients from Bulgaria, 15 from Croatia, 48 from the Czech Republic, 22 from France, 33 from Hungary, 30 from Poland, 7 from Romania, and 1 from Spain). Serbia recruited 46 patients.

Details of patient disposition can be found in ***Table 4***.

Table 4 – Patient Disposition

Parameter	**Cariprazine**	**Risperidone**	**Overall**
Study Populations	N (%)	N (%)	N (%)
Screened			533 (100)
Randomized	230 (43.2)	231 (43.3)	461 (86.5)
Safety	230 (43.2)	230 (43.2)	460 (86.3)
ITT	227 (42.6)	229 (43.0)	456 (85.6)
Study Completion (safety population)	N=230 n (%)	N=230 n (%)	N=460 n (%)
Completed double-blind treatment period (baseline to Week 26)	178 (77.4)	178 (77.4)	356 (77.4)
Completed study, including safety follow-up period (baseline to Week 28)	177 (77.0)	178 (77.4)	355 (77.2)
Study Treatment Continuation (safety population)	N=230 n (%)	N=230 n (%)	N=460 n (%)
Week 1	222 (96.5)	226 (98.3)	448 (97.4)
Week 2	221 (96.1)	222 (96.5)	443 (96.3)
Week 3	214 (93.0)	218 (94.8)	432 (93.9)

Parameter	Cariprazine	Risperidone	Overall
Week 4	216 (93.9)	214 (93.0)	430 (93.5)
Week 6	211 (91.7)	211 (91.7)	422 (91.7)
Week 10	199 (86.5)	204 (88.7)	403 (87.6)
Week 14	184 (80.0)	191 (83.0)	375 (81.5)
Week 18	180 (78.3)	186 (80.9)	366 (79.6)
Week 22	177 (77.0) [f]	183 (79.6)	360 (78.3)
Week 26 (completed treatment)	178 (77.4) [f]	178 (77.4)	356 (77.4)
Early Termination (safety population)	N=230 n (%)	N=230 n (%)	N=460 n (%)
During double-blind treatment period	52 (22.6)	52 (22.6)	104 (22.6)
During up-titration phase	8 (3.5)	4 (1.7)	12 (2.6)
During treatment continuation phase	44 (19.1)	48 (20.9)	92 (20.0)
Reasons for Early Termination in Decreasing Order by Frequency Overall (safety population)	N=230 n (%)	N=230 n (%)	N=460 n (%)
Early termination from the double-blind period	52 (22.6)	52 (22.6)	104 (22.6)
Adverse event	22 (9.6)	25 (10.9)	47 (10.2)
Patient withdrew consent	15 (6.5)	15 (6.5)	30 (6.5)
Other	5 (2.2)	7 (3.0)	12 (2.6)
Noncompliance	3 (1.3)	2 (0.9)	5 (1.1)
Insufficient therapeutic response	2 (0.9)	2 (0.9)	4 (0.9)
Protocol violation	3 (1.3)	0	3 (0.7)
Lost to follow up	2 (0.9)	1 (0.4)	3 (0.7)

ITT = intent-to-treat; N = number of patients overall; n (%) = number and percent of patients in the sample

The following demographic data are related to the safety population. The median age of entry into the study was 40.0 years, ranging from 19 to 65 years. The sex ratio was 57.4% male and 42.6% female; more men were randomized to the risperidone group, although without statistically significant difference when compared to the cariprazine group. The main demographic characteristics are summarized in ***Table 5***.

Table 5 – Demographic Characteristics, Safety Population

Parameter	Cariprazine N=230	Risperidone N=230	Overall N=460	P-Value Between Treatments*
Age at screening (years)				0.797
Mean ± SD	40.2 ± 10.5	40.7 ± 11.2	40.4 ± 10.8	
Median	39.5	40.0	40.0	
Minimum, maximum	19, 65	19, 64	19, 65	
Sex	n (%)	n (%)	n (%)	0.152
Male	124 (53.9)	140 (60.9)	264 (57.4)	
Female	106 (46.1)	90 (39.1)	196 (42.6)	
Race	n (%)	n (%)	n (%)	NA
White	221 (96.1)	217 (94.3)	438 (95.2)	
Black or African American	0	0	0	
Asian	0	0	0	
Not recorded	9 (3.9)	13 (5.7)	22 (4.8)	

N = number of patients overall; n (%) = number and percent of patients in the sample; NA = not applicable

** Comparability between treatment groups was tested using an analysis of variance model, with treatment group and study center as the factors for continuous variables and the Cochran-Mantel-Haenszel test, controlling for study center, for categorical variables.*

With regard to schizophrenia history, the baseline characteristics of the 2 treatment arms were comparable. Overall, the most frequent type of schizophrenia was paranoid (384 patients, 83.5%). Other forms were less frequent: residual 36 (7.8%), undifferentiated 29 (6.3%), disorganized 10 (2.2%), and catatonic 1 (0.2%).

The median age of schizophrenia duration was 10.1 years (between 2.0 - 42.8 years), with the majority of patients having less than 5 exacerbations (274 patients, 59.6%), 140 patients (30.4%) had 5-10 exacerbations, 31 patients (6.7%) 11-15 exacerbations and only 15 patients (3.3%) had more than 15 acute episodes. Details of the patients' schizophrenia history can be found in ***Table 6***.

Table 6 – Schizophrenia History, Safety Population

Parameter	Cariprazine N=230	Risperidone N=230	Overall N=460
Schizophrenia Type	n (%)	n (%)	n (%)
Paranoid	188 (81.7)	196 (85.2)	384 (83.5)
Residual	24 (10.4)	12 (5.2)	36 (7.8)
Undifferentiated	13 (5.7)	16 (7.0)	29 (6.3)
Disorganized	4 (1.7)	6 (2.6)	10 (2.2)
Catatonic	1 (0.4)	0	1 (0.2)
Time from Diagnosis to Date of Informed Consent (years), n	n=230	n=230	n=460
Mean ± SD	11.98 ± 8.1	12.96 ± 9.2	12.47 ± 8.7
Median	9.8	10.2	10.1
Minimum, maximum	2, 39.2	2, 42.8	2, 42.8
Number of Acute Exacerbations	n (%)	n (%)	n (%)
< 5	148 (64.3)	126 (54.8)	274 (59.6)
5-10, inclusive	61 (26.5)	79 (34.3)	140 (30.4)
11-15, inclusive	11 (4.8)	20 (8.7)	31 (6.7)
> 15	10 (4.3)	5 (2.2)	15 (3.3)
Time from Recovery from Last Acute Exacerbation to Date of Informed Consent (years), n	n=228	n=230	n=458
Mean ± SD	3.46 ± 3.3	3.15 ± 2.9	3.30 ± 3.2
Median	2.25	2.05	2.10
Minimum, maximum	0.5, 21.9	0.5, 16.9	0.5, 21.9
Number of Psychiatric Hospitalizations * in the Last 12 Months, n	n=230	n=230	n=460
Mean ± SD	0.3 ± 1.5	0.2 ± 0.5	0.3 ± 1.1
Median	0.0	0.0	0.0
Minimum, maximum	0, 22	0, 2	0, 22
Time from Last Psychiatric Hospitalization * to Date of Informed Consent (years), n	n=220	n=223	n=443
Mean ± SD	3.79 ± 3.8	3.96 ± 3.9	3.88 ± 3.9
Median	2.35	2.50	2.40
Minimum, maximum	0, 30.4	0, 26.6	0, 30.4

Parameter	Cariprazine N=230	Risperidone N=230	Overall N=460
Duration of Last Psychiatric Hospitalization * (days), n	n=227	n=229	n=456
Mean ± SD	53.3 ± 49.6	80.9 ± 206.2	67.2 ± 150.7
Median	40.0	45.0	43.0
Minimum, maximum	0, 347	0, 2842	0, 2842

N = number of patients overall; n (%) = number and percent of patients in the sample
**Data were included for any kind of psychiatric hospitalization, not only for an acute exacerbation*

4.2. Primary Efficacy Endpoint – PANSS Factor Score for Negative Symptoms

The primary efficacy parameter was change from baseline to endpoint (Week 26/ET) on the PANSS-FSNS, using the MMRM approach.

The LS mean CfB at Week 26 were -8.9 and -7.4 for cariprazine and risperidone, respectively. The pairwise difference was -1.5 (95% CI: -2.4, -0.5), with a P value of 0.002 (***Figure 8***).

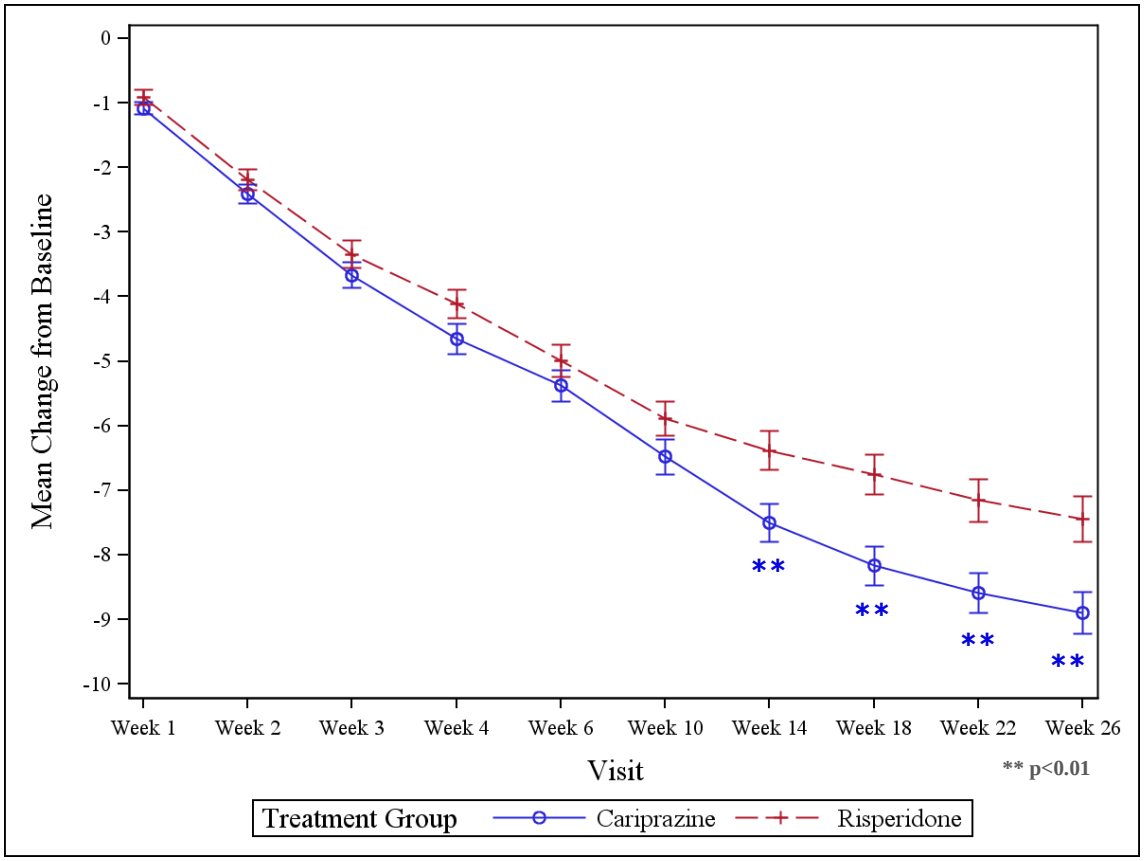


Figure 8 – Mean Treatment Profiles for the Change from Baseline (± SE) in PANSS Factor Score for Negative Symptoms (MMRM), ITT Population

ITT = intent to treat; MMRM = mixed-effects model for repeated measures; PANSS = Positive and Negative Syndrome Scale; SE = standard error

Scores on the PANSS total score for negative symptoms ranged from 7 to 49; a lower score was favorable.

On Week 14 and onwards, there was statistically significant difference between the treatment arms, favoring the cariprazine arm, as detailed in ***Table 7***.

Table 7 – Primary Endpoint: Repeated Measures ANCOVA Mixed-Effects Model on the Change from Baseline to Week 26 (Endpoint) in the PANSS Factor Score for Negative Symptoms, ITT Population

Visit	Treatment	Least Squares Mean [a, b]	Standard Error of Least Squares Mean	Mean Difference Between Cariprazine and Risperidone	2-Sided 95% CI for Mean Difference	P-value
Week 1	Cariprazine	-1.1	0.1	-0.2	(-0.5, 0.1)	0.240
	Risperidone	-0.9	0.1			
Week 2	Cariprazine	-2.4	0.2	-0.2	(-0.6, 0.2)	0.302
	Risperidone	-2.2	0.2			
Week 3	Cariprazine	-3.7	0.2	-0.3	(-0.9, 0.2)	0.260
	Risperidone	-3.3	0.2			
Week 4	Cariprazine	-4.7	0.2	-0.5	(-1.2, 0.1)	0.095
	Risperidone	-4.1	0.2			
Week 6	Cariprazine	-5.4	0.3	-0.4	(-1.1, 0.3)	0.264
	Risperidone	-4.9	0.3			
Week 10	Cariprazine	-6.5	0.3	-0.6	(-1.3, 0.2)	0.116
	Risperidone	-5.9	0.3			
Week 14	Cariprazine	-7.5	0.3	-1.1	(-1.9, -0.3)	0.008**
	Risperidone	-6.4	0.3			
Week 18	Cariprazine	-8.2	0.3	-1.4	(-2.3, -0.6)	0.001**
	Risperidone	-6.8	0.3			
Week 22	Cariprazine	-8.6	0.3	-1.4	(-2.3, -0.6)	0.002**
	Risperidone	-7.2	0.3			
Week 26	Cariprazine	-8.9	0.3	-1.5	(-2.4, -0.5)	0.002**
	Risperidone	-7.4	0.4			

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat, PANSS=Positive and Negative Symptom Scale
The PANSS factor score for negative symptoms ranged from 7 to 49, a lower score was favorable.

The sensitivity analysis based on an ANCOVA model using the LOCF approach on the primary endpoint also showed a statistically significant difference in favor of cariprazine over risperidone. The LS mean CfB to Week 26/ET on the PANSS-FSNS were 8.1 and

6.8 for cariprazine and risperidone, respectively. The pairwise difference was 1.3 (95% CI: -2.2, 0.5) with a P value of 0.003.

4.3. Secondary Efficacy Endpoint – Personal and Social Performance Scale

The secondary efficacy parameter was change from baseline to endpoint (Week 26/ET) on the PSP total score, using the MMRM approach. The LS mean CfB at Week 26 were 14.3 and 9.7 for cariprazine and risperidone, respectively. The pairwise difference was 4.6 (95% CI: 2.7, 6.6), with a P value of 0.001 (***Figure 9***).

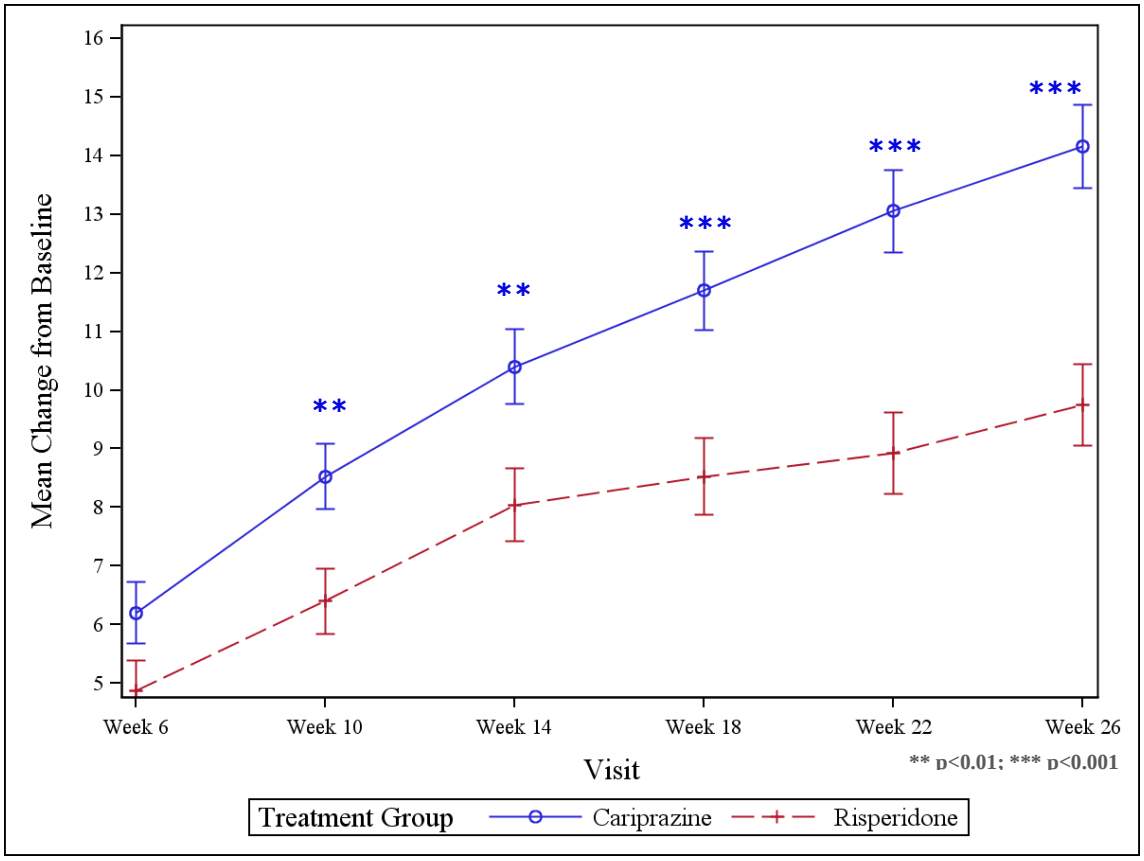


Figure 9 – Mean Treatment Profiles (± SE) for the Change from Baseline in the PSP Score (MMRM), ITT Population

ITT = intent to treat; MMRM = mixed-effects model for repeated measures; PSP = Personal and Social Performance scale; SE = standard error

The PSP score ranged from 1 to 100, a higher score was favorable.

On Week 10 and onwards, there was statistically significant difference between the treatment arms, favoring the cariprazine arm, as detailed in ***Table 8***.

Table 8 - Secondary Endpoint: Repeated Measures ANCOVA Mixed-Effects Model on the Change from Baseline to Week 26 (Endpoint) in the PSP Score, ITT Population

Visit	Treatment	Least Squares Mean	Standard Error of Least Squares Mean	Mean Difference between Cariprazine and Risperidone	2-Sided 95% CI for Mean Difference	P-Value
Week 6	Cariprazine	6.3	0.5	1.4	(-0.0, 2.8)	0.056
	Risperidone	4.9	0.5			
Week 10	Cariprazine	8.6	0.5	2.2	(0.7, 3.7)	0.005**
	Risperidone	6.4	0.6			
Week 14	Cariprazine	10.5	0.6	2.5	(0.8, 4.2)	0.005**
	Risperidone	8.0	0.7			
Week 18	Cariprazine	11.8	0.6	3.3	(1.5, 5.1)	<0.001 ***
	Risperidone	8.5	0.7			
Week 22	Cariprazine	13.2	0.7	4.3	(2.4, 6.2)	<0.001 ***
	Risperidone	8.9	0.7			
Week 26	Cariprazine	14.3	0.6	4.6	(2.7, 6.6)	<0.001 ***
	Risperidone	9.7	0.8			

ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent to treat; PSP=Personal and Social Performance scale
PSP Scores ranged from 1 to 100, a higher score was favorable.

The sensitivity analysis based on an ANCOVA model using the LOCF approach on the secondary endpoint also showed a statistically significant difference in favor of cariprazine over risperidone. The LS mean CfB to Week 26/ET on the PSP total score were 12.7 and 9.0 for cariprazine and risperidone, respectively. The pairwise difference was 3.7 (95% CI: 1.7, 5.6) with a P value of <0.001.

4.4. Additional Efficacy Endpoints of Interest

4.4.1. CGI-S and CGI-I

For the CGI-S and CGI-I analyses the same MMRM approach was applied to assess change from baseline to endpoint (Week 26/ET). The CGI-S LS mean CfB at Week 26 were 0.9 and 0.7 for cariprazine and risperidone, respectively. The pairwise difference was -0.2 (95% CI: -0.4, -0.1), with a P value of 0.005. The CGI-I LS means at Week 26 were 2.5 and 2.9 for cariprazine and risperidone, respectively. The pairwise difference was -0.4 (95% CI: -0.6, -0.2), with a P value of <0.001. The changes over time in CGI-S and mean treatment profiles on the CGI-I are shown on ***Figure 10*** and ***Figure 11***.

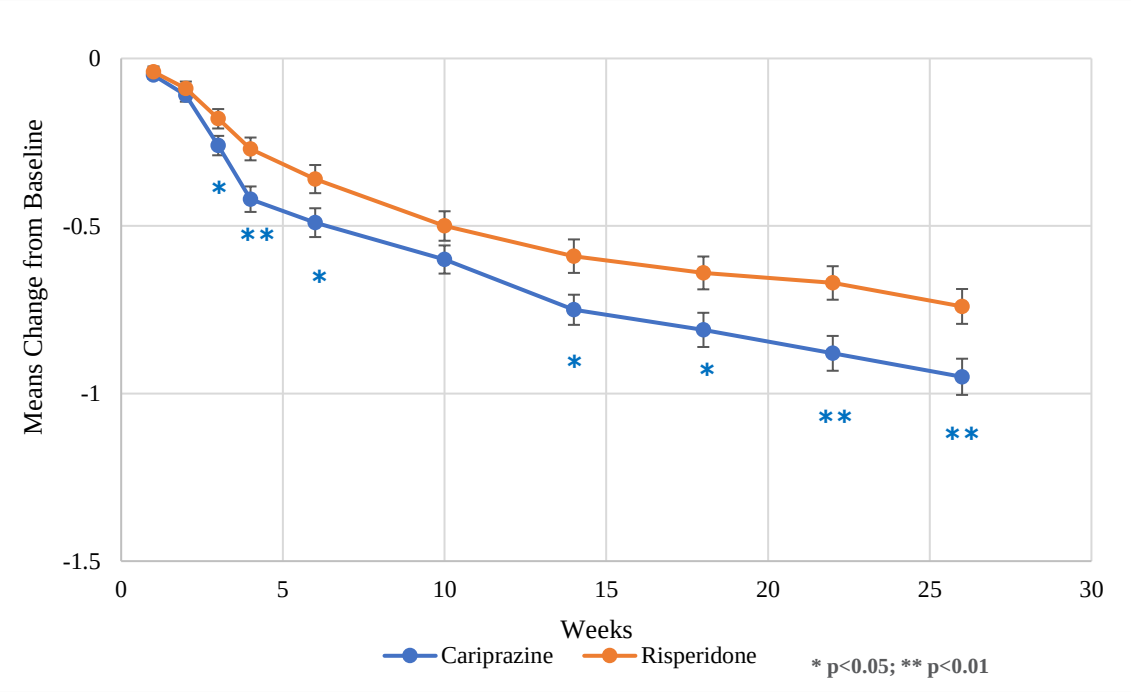


Figure 10 – Mean Treatment Profiles (± SE) for the Change from Baseline in the CGI-S Score (MMRM), ITT Population

ITT = intent to treat; MMRM = mixed-effects model for repeated measures; CGI-S = Clinical Global Impression - Severity; SE = standard error

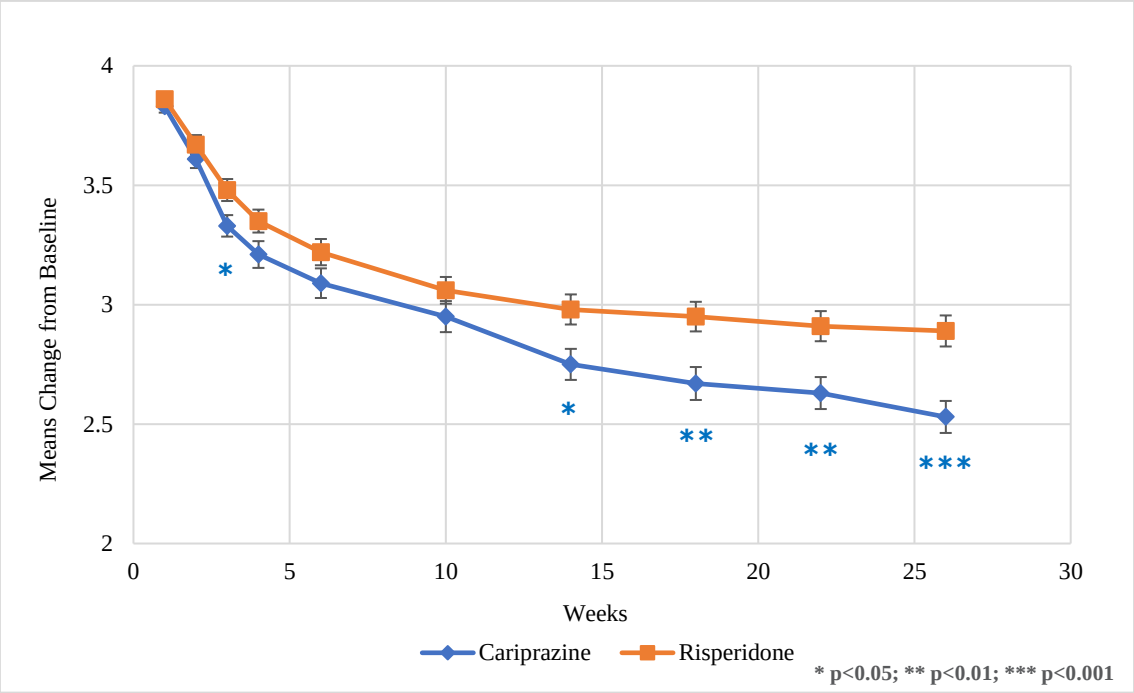


Figure 11 – Mean Treatment Profiles (± SE) for the CGI-I Score (MMRM), ITT Population

ITT = intent to treat; MMRM = mixed-effects model for repeated measures; CGI-I = Clinical Global Impression - Improvement; SE = standard error

4.4.2. PANSS Total Score

The PANSS total score was also analyzed with the same MMRM methodology. The PANSS total score LS mean CfB at Week 26 were -16.9 and -14.8 for cariprazine and risperidone, respectively. The pairwise difference was -2.1 (95% CI: -4.3, 0.1), with a P value of 0.065.

4.4.3. PSP Subdomains

The PSP scale consists of 4 subdomains, representing various areas of patient functioning: socially useful activities, personal and social relationships, self-care, disturbing and aggressive behavior. LS mean CfB scores and LS mean differences were also calculated for these subdomains with the MMRM approach (***Figure 12***).

At Week 26, the least squares mean CfB in the PSP socially useful activities area scores were -0.95 for cariprazine and -0.60 for risperidone. The pairwise difference was -0.35 (95% CI: -0.50, -0.20). Cariprazine showed a more favorable CFB from Week 6 to Week 26, with statistically significant differences observed at Weeks 18 (P = 0.004), 22 (P = 0.003), and 26 (P < 0.001).

At Week 26, the least squares mean CfB in the PSP personal and social relationships area scores were -0.85 for cariprazine and -0.61 for risperidone. The pairwise difference was -0.24 (95% CI: -0.37, -0.10; P < 0.001). Cariprazine showed a more favorable CfB from Week 6 onward, with statistically significant differences at each follow-up visit where the scale was measured.

The LS mean CfB in the PSP self-care area scores at Week 26 were -0.70 for cariprazine and -0.50 for risperidone. The pairwise difference was -0.20 (95% CI: -0.34, -0.06). The CfB favored cariprazine from Week 10 onward, with statistically significant differences at Weeks 22 (P = 0.023) and 26 (P = 0.004).

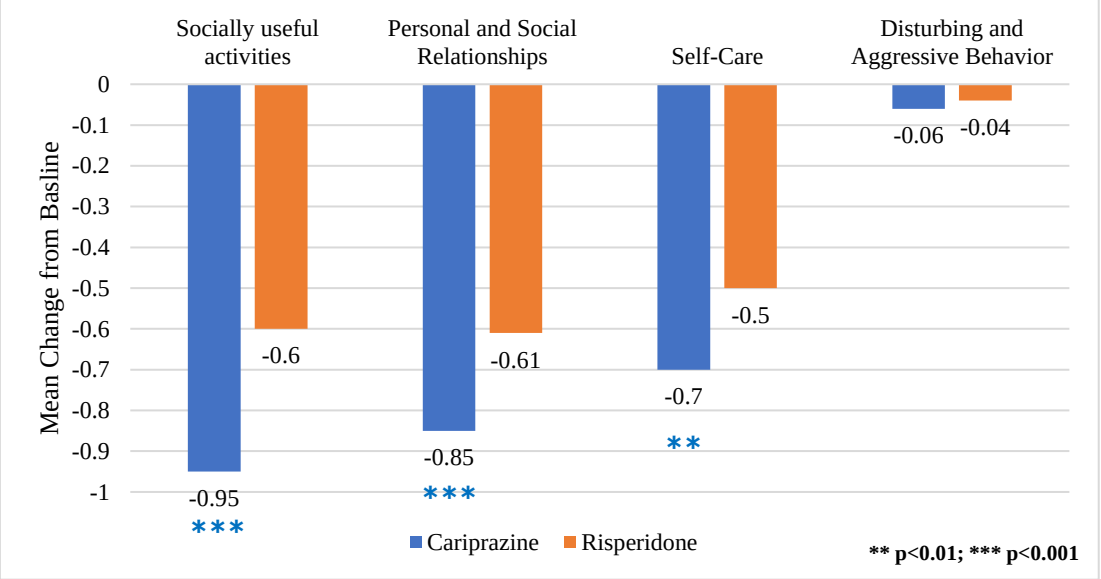


Figure 12 – Change from Baseline to Week 26 (Endpoint) in the PSP Subdomains, ITT Population

4.5. Pseudospecificity Analyses

The goal of the pseudospecificity analyses was to assess if the improvements seen on the primary endpoint can be attributed to improvement to primary negative symptoms or was it influenced by other secondary factors, such as improvement on positive or depressive symptoms.

4.5.1. PANSS Factor Score for Positive Symptoms

The change from baseline to endpoint (Week 26/ET) on the PANSS-FSPS was assessed by utilizing the same MMRM approach as for the other parameters. The baseline mean PANSS-FSPS was low in both arms, 8.7 and 8.6 in the cariprazine and risperidone groups, respectively. The LS mean CfB at Week 26 were -1.1 for both treatment arms. The pairwise difference was therefore 0.0 (95% CI: -0.4, 0.5), with a P value of 0.963 (***Figure 13***).

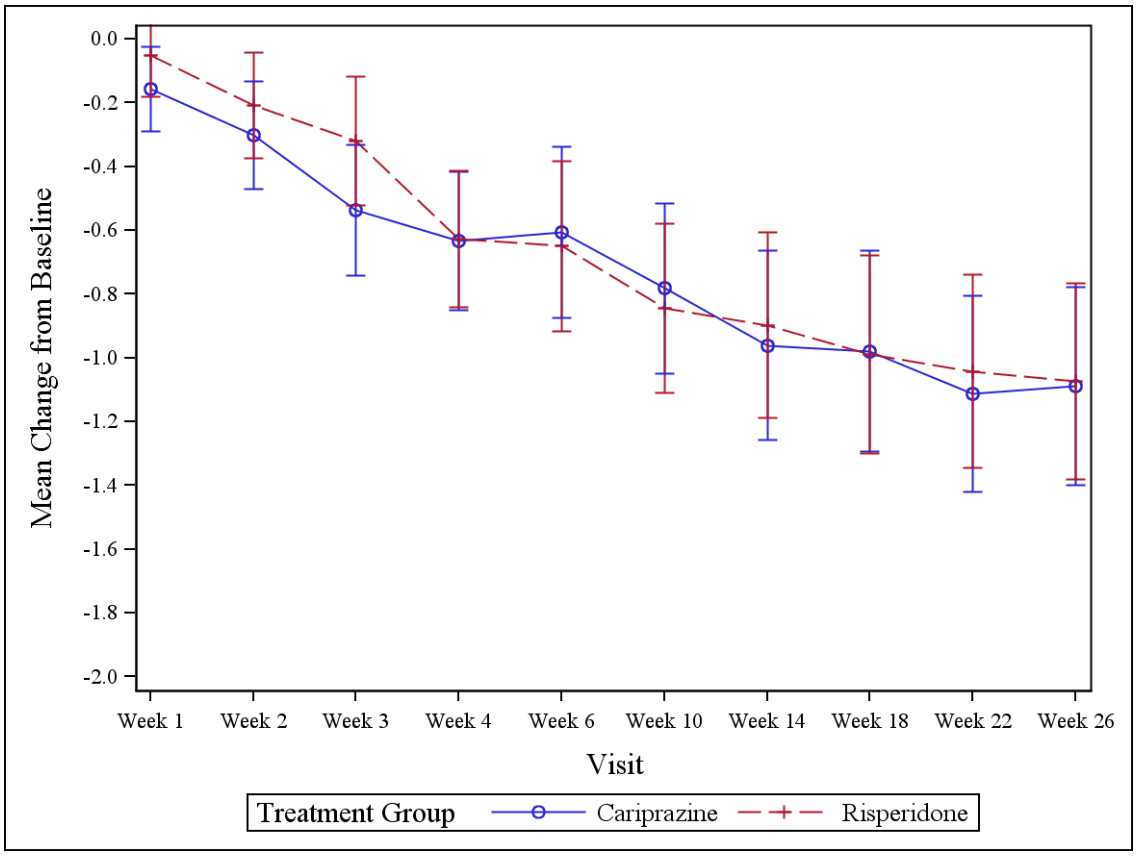


Figure 13 – Change from Baseline (± SE) to Week 26 in the PANSS Factor Score for Positive Symptoms, ITT Population
ITT = intent to treat; PANSS = Positive and Negative Syndrome Scale; SE = standard error

4.5.2. Calgary Depressions Scale for Schizophrenia

The other pseudospecificity endpoint was the change from baseline to endpoint (Week 26/ET) on the CDSS, using the MMRM approach. Due to the exclusion criteria, the baseline CDSS scores were low on both arms. The LS mean CfB at Week 26 were -0.3 and -0.2 for cariprazine and risperidone, respectively, with an LS mean difference of -0.1, without statistical difference (P = 0.658), ***Figure 14***.

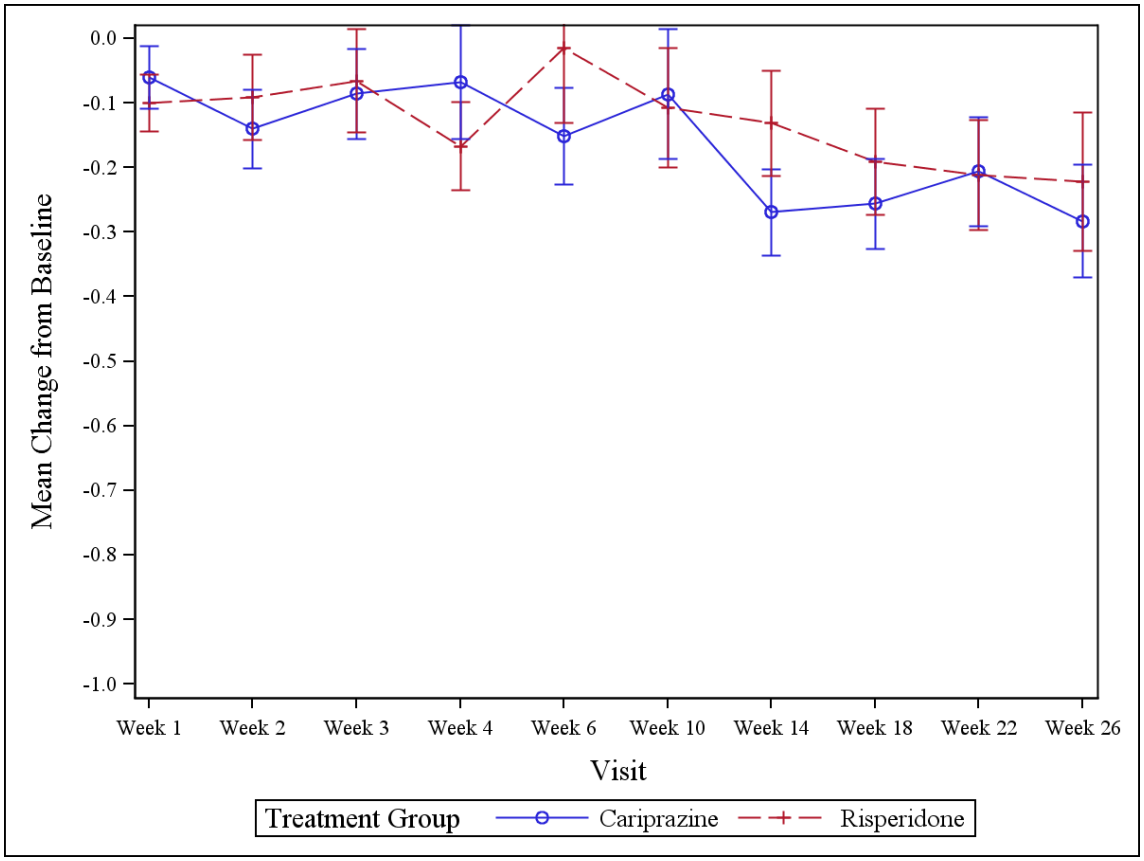


Figure 14 – Change from Baseline (± SE) to Week 26 in the CDSS Total Score, ITT Population

CDSS = Calgary Depression Scale for Schizophrenia; ITT = intent to treat; SE = standard error

CDSS scores ranged from 0 to 27, a lower score was favorable.

4.6. Safety Assessments

Due to the main focus of this thesis, only selected safety endpoints will be discussed that are the most relevant for understanding the profile of a D3/D2 partial agonist.

4.6.1. Overview of Adverse Events

Adverse events were collected throughout the entire study from the time point of signing the ICF. However, for analysis purposes only the treatment-emergent adverse events will be considered, defined as any adverse events initiated after the first dose of IMP or already present before but worsened. The following analyses are performed on the safety population.

An overview of the adverse events recorded during the study is in ***Table 9***.

Table 9 – Summary of Adverse Events, Safety Population

Parameter	Cariprazine N=230	Risperidone N=230	Overall N=460
Patients with any AE during study, n (%)[a]	134 (58.3)	140 (60.9)	274 (59.6)
Number of AEs reported during the study, n	295	350	645
Patients with any AE during the DB treatment period, n (%)	123 (53.5)	131 (57.0)	254 (55.2)
Number of AEs reported during the DB treatment period, n	270	317	587
Patients with any AE during the safety follow-up period, n (%) [b]	7 (3.5)	3 (1.5)	10 (2.5)
Number of AEs reported during the safety follow-up period, n	7	3	10
Patients with any AE related to study IMP during the study, n (%) [c]	84 (36.5)	95 (41.3)	179 (38.9)
Number of AEs related to study IMP reported during study, n	151	178	329
Patients with maximum severity of any AE during study: n (%) [c]			
Mild	72 (31.3)	74 (32.2)	146 (31.7)
Moderate	55 (23.9)	55 (23.9)	110 (23.9)
Severe	7 (3.0)	11 (4.8)	18 (3.9)

Parameter	Cariprazine N=230	Risperidone N=230	Overall N=460
Deaths during the DB treatment period, n (%)	0	1 (0.4)	1 (0.2)
Patients with any non-fatal SAE during the DB treatment period, n (%)	7 (3.0)	7 (3.0)	14 (3.0)
Patients with any non-fatal SAE during the safety follow-up period, n (%)	2 (1.0)	0	2 (0.5)
Patients discontinued from the study due to an AE during the study, n (%)	23 (10.0)	27 (11.7)	50 (10.9)
Patients discontinued from the study due to an SAE during the study, n (%)	5 (2.2)	7 (3.0)	12 (2.6)

AE = adverse event; DB = double blind; IMP = investigational medicinal product; N = number of patients overall; n (%) = number and percent of patients in the sample; SAE = serious adverse event

a The terminology, "during the study" refers to the double-blind and safety follow-up periods.

b The safety follow-up period consisted of 1 to 14 days following the date of Visit 13 or early termination, or at least 30 days for an SAE.

c Continuous AEs reported separately under different severities are counted as 1 report. If more than 1 AE was coded to the same preferred term for the same patient, the patient was counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the IMP.

The number patients who experienced TEAEs during the double-blind period of the study were comparable, 53.5 and 57.0% on the cariprazine and risperidone groups, respectively. If we look at the TEAEs related to the study drug, slightly fewer patients experienced such adverse events on the cariprazine treatment arm (36.5%) compared to the risperidone arm (41.3%). There was 1 death case during the study on the risperidone arm, however, that was not related to the study drug or interventions (brain tumor and pulmonary carcinoid tumor).

The most frequent adverse events reported during the double-blind treatment period are summarized in ***Table 10***.

Table 10 - Incidence of Treatment-Emergent Adverse Events in ≥ 3% of Patients by Preferred Term, in Any Treatment Group, during the Double-Blind Period by MedDRA System Organ Class and Preferred Term, Safety Population

MedDRA System Organ Class Preferred Term	**Cariprazine N=230 n (%)**	**Risperidone N=230 n (%)**
Any TEAE during the double-blind treatment period	123 (53.5)	131 (57.0)
Nervous system disorders	57 (24.8)	67 (29.1)
Akathisia	19 (8.3)	12 (5.2)
Cogwheel rigidity	4 (1.7)	8 (3.5)
Dizziness	4 (1.7)	11 (4.8)
Headache	13 (5.7)	24 (10.4)
Somnolence	9 (3.9)	13 (5.7)
Psychiatric disorders	57 (24.8)	56 (24.3)
Anxiety	13 (5.7)	11 (4.8)
Insomnia	21 (9.1)	23 (10.0)
Schizophrenia	15 (6.5)	10 (4.3)
Gastrointestinal disorders	24 (10.4)	20 (8.7)
Nausea	9 (3.9)	6 (2.6)
General disorders and administration site conditions	14 (6.1)	21 (9.1)
Fatigue	5 (2.2)	10 (4.3)
Infections and Infestations	12 (5.2)	16 (7.0)
Nasopharyngitis	3 (1.3)	7 (3.0)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients overall; n (%) = number (percent) of patients in the sample, TEAE = treatment-emergent adverse event

Looking at the relatedness, the adverse events that were reported in at least 5% of patients in either of the treatment groups were: akathisia (7.8% and 4.8%), insomnia (5.2% and 5.2%), and headache (3.0% and 6.1%) in the cariprazine and risperidone groups, respectively.

Adverse events leading to discontinuation were reported in 23 (10.0%) and 27 (11.7%) patients in the cariprazine and risperidone treatment arms, respectively. The most common AEs leading the premature termination were schizophrenia, insomnia, and akathisia.

4.6.2. Scales Assessing the Extrapyramidal Symptoms

Three scales were used in the study to assess the extrapyramidal symptoms that are one of the most critical and unwanted side effects of antipsychotic drugs acting on the dopaminergic system.

The Abnormal Involuntary Movement Scale (AIMS) is a scale to assess the involuntary movements associated with antipsychotic treatment, measuring facial, oral, extremities and trunk movements. It consists of 12 items, including 2 questions about dental status that are not rated for severity. (75)

The Barnes Akathisia Rating Scale (BARS) measures drug-induced akathisia on a 4-item scale, including observation, self-aware and distress associated with akathisia and an overall severity question. (76)

The Simpson-Angus Scale is a 10-item scale for the assessment of parkinsonism associated with antipsychotic use. (77) Items are measuring gait, rigidity, glabella tap, tremor and salivation.

All of the above scales were used to assess the extrapyramidal symptoms during the study. On the AIMS, at Week 26/ET, the mean total scores were showing no to mild symptoms, means ranging between 0.1 and 0.2, in the cariprazine and risperidone groups, respectively. No clinically meaningful differences between treatment groups were detected throughout the study (***Figure 15***).

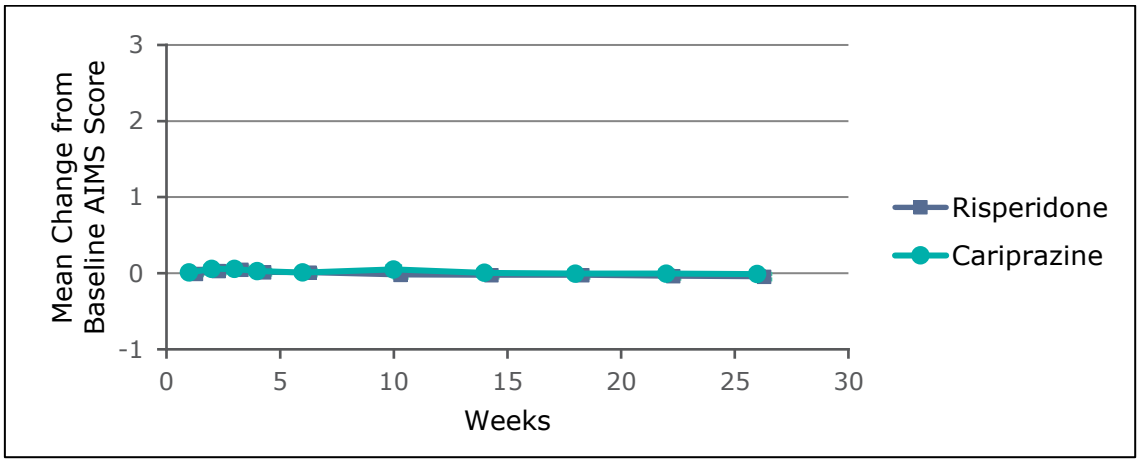


Figure 15 – Change from Baseline to Week 26 in the AIMS Score

On the BARS, there were really few patients reporting distress related the akathisia (10 patients on both treatment arms, mild to moderate intensity). When looking at the BARS

total scores, there were low changes throughout the study with no difference between the treatment groups (***Figure 16***).

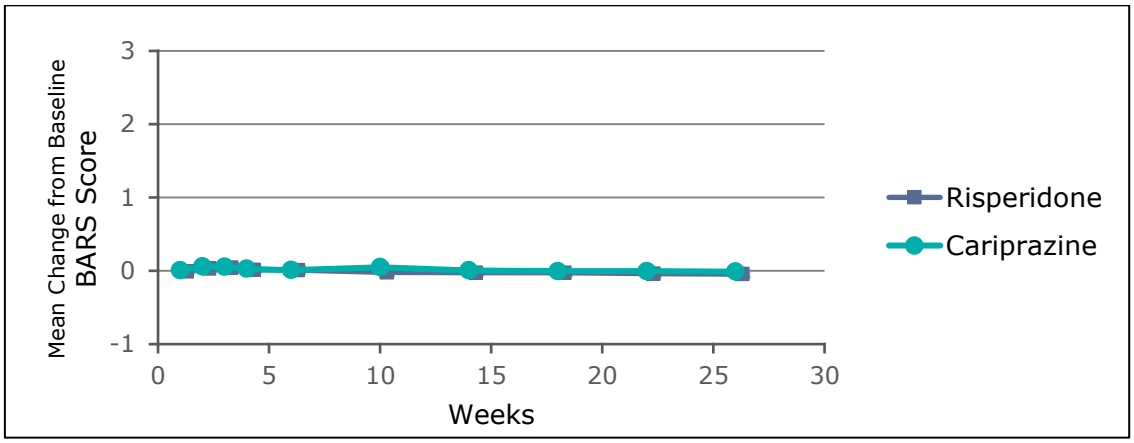


Figure 16 – Change from Baseline to Week 26 in the BARS Score

The third scale assessing the extrapyramidal symptoms – the SAS – showed also no to mild symptoms of parkinsonism at Week 26/ET (0.4 and 0.6 on the cariprazine and risperidone arms, respectively), and practically no change from baseline (-0.0 and 0.1 in the cariprazine and risperidone groups, respectively) as shown on ***Figure 17***.

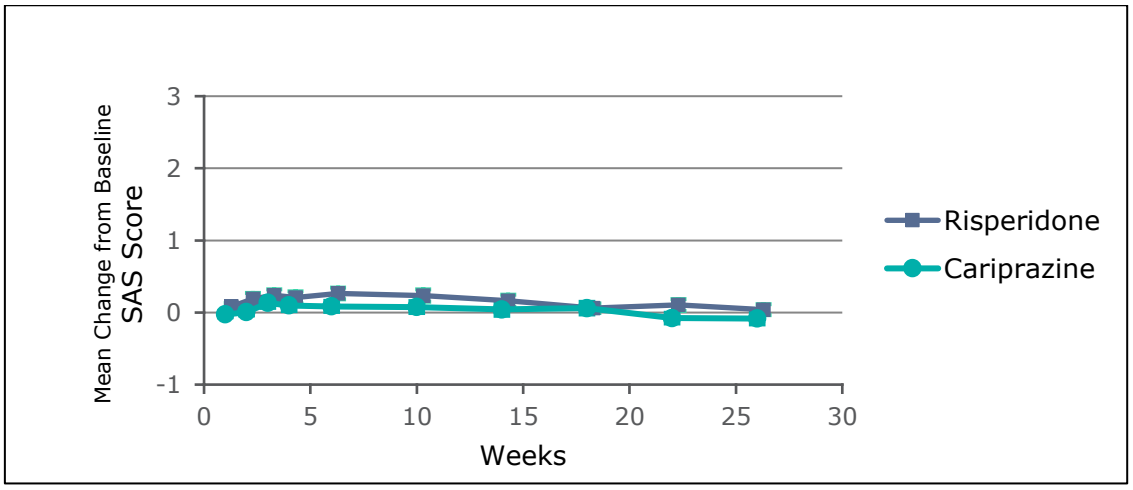


Figure 17 – Change from Baseline to Week 26 in the SAS Score

5. DISCUSSION

RGH-188-005 was the first large-scale, appropriately designed randomized clinical trial that compared two atypical antipsychotic drugs in monotherapy, one of which has a well-established efficacy and has been a gold standard in schizophrenia. The primary analysis using the PANSS-FSNS showed statistically significant improvement on the cariprazine arm when compared to risperidone This has been also reconfirmed in the sensitivity analyses, and the improvements on the overall global scores (CGI-S, CGI-I). However, what is even more important, is the fact that not only the symptomatology improved, but the patient functionality as well, measured on the PSP. This translates to better daily living, more independence, and less burden for the patient's family.

My objective to identify the most suitable endpoint for evaluating an antipsychotic's efficacy in treating predominant, primary negative symptoms was validated, as all efficacy endpoints, including sensitivity analyses, consistently indicated the same outcome.

On the primary endpoint there was a difference of 1.5 points. Given the fact that the PANSS-FSNS ranges between 7-35, the clinical relevance might be questioned of such a finding. There are 2 methodologies to address the clinical relevance: looking at the effect sizes comparing the 2 treatment arms, and calculating the Number Needed to Treat (NNT).

If we look at the effect sizes on both primary and secondary endpoints for the cariprazine arm, they are 0.31 and 0.48, respectively. Although in general an effect size of 0.2 is considered as low, 0.5 as medium and 0.8 as large, it has been widely observed that effect sizes in psychiatric conditions tend to be lower than for other indications. (78) Furthermore, these effect sizes in psychiatry are comparing a test compound to placebo, while our study compared cariprazine to an effective active comparator, risperidone. (79) It also adds to the relevance that the patient functionality improved with an even larger effect size.

We measured the NNT in terms of responders on the PANSS-FSNS (20% improvement compared to baseline): how many patients one has to treat to increase the number of responders by 1. Based on the study data the NNT for the 20% responder rate was 9,

while using the even more strict threshold of 30%, the NNT decreased to 8. (71) In general, an NNT of ≤10 is considered clinically relevant. (80)

5.1. Appropriateness of the Clinical Trial Design

In 2012, there was an international meeting held in Florence, Italy, with the participation of academia, industry and the EMA. (81) The aim of this meeting was to discuss the methodological issues with clinical trials assessing negative symptoms of schizophrenia. Before the meeting, participants had been to submit questions that they had found relevant and unresolved which was then distributed as part of a survey. Some topics were already agreed based on the initial results of the survey and were not discussed at the meeting. If there was disagreement among the answers, individuals having different position were asked to present their standpoint at the meeting, supported by available data. The consensus from this meeting is considered as the gold standard in terms of methodology in studies assessing the negative symptoms.

Although at the time point of the study design the above paper has not yet been issued, topics that had been addressed during this meeting provide an opportunity to evaluate the appropriateness and limitations of study RGH-188-005. These aspects were rediscussed by the Negative Symptoms Work Group from the International Society of CNS Clinical Trails and Methodology in 2018 that reconfirmed the validity of the methodological recommendations from 2012. (82)

5.1.1. Criteria Affecting Patient Selection

One of the most important criteria are related to magnitude of the negative symptoms. The consensus was that the patients should show at least 2 negative symptoms, out of one should be rated at least moderate in severity. (81) Based on the inclusion criteria in our study, patients had to have at least 4 points on at least 2 PANSS items related to negative symptoms to be eligible. Furthermore, it was also discussed whether patients with predominant or prominent negative symptoms should be included in such trials. (81,83) The definition of predominant negative symptoms is when positive symptoms are low and do not add to the patient's burden, while negative symptoms are still high. It is considered as prominent negative symptoms when both negative and positive symptoms

contribute to the patient overall clinical status. There was no clear agreement whether the patient population should be restricted to predominant patients only, except for the fact that including patients with prominent symptoms increases variability and decreases the likelihood to show an effect. Based on my extensive evaluation of all available data at the timepoint of writing the study protocol, my recommendation was to include only patients with predominant negative symptoms in RGH-188-005.

Retrospectively this proved to be the better population to examine negative symptoms patients. In an article by Krause et al, authors suggest that using "predominant negative symptoms" as an inclusion criterion provides a better safeguard against secondary negative symptoms compared to using "prominent negative symptoms." (84) In the prominent negative symptom subpopulation, the effects on primary negative symptoms are more difficult to separate from effects on other symptoms. Studies enrolling patients with prominent negative symptoms showed that the reduction of negative symptoms might be secondary to effects on other symptoms, particularly positive symptoms. In contrast, the “predominant negative symptoms” criterion ensures that patients have more negative symptoms than positive symptoms, with a low level of positive symptoms that cannot further improve significantly. This makes it easier to observe the effects of antipsychotics on negative symptoms without the confounding influence of improvements in other symptom domains.

The other important criterion was to exclude patients with significant extrapyramidal side effects due to antipsychotic medication as these symptoms can also mimic negative symptoms. (81) Hence, I proposed an exclusion criterion for the patients: any clinically relevant parkinsonian symptoms judged by the Investigator or a score of >3 on the first 8 items of the SAS.

Also, the exclusion of patients with depressive symptoms were discussed, again to exclude secondary negative symptoms related to depressive symptoms. (81) The overall conclusion was that patients should be excluded with comorbid depression. However, the applied tool should be carefully selected. E.g. Hamilton Depression Rating Scale should not be used to exclude patients with depressive symptoms, as this tool does not correctly handle the overlap between the two conditions (depression and negative symptoms of schizophrenia) and would exclude patients with negative symptoms as well. The

recommendation of the board was to use the Calgary Depression Rating Scale instead which is found to be more appropriate, which again confirmed the choice of assessment tool to select the right patient population in our study.

There was also a debate on the upper age limit for such trials. (81) In general, 65 years would be the preferred cut-off also for regulatory reasons, however, negative symptoms are also predominant in the younger age population (prodromal symptoms of schizophrenia) and the elderly (residual symptoms of schizophrenia). (85–87) In our study, the average age of the patients was around 40 years in both treatment groups.

5.1.2. Appropriate Duration of the Trial

One of the key challenges of such trials is the study duration. There are various factors to be considered. On one hand, if the study is too short, the investigated drug(s) will not have sufficient time to develop maximum effect. On the other hand, a study duration too long will increase the number of drop-outs, as well as the study costs. It was concluded, that for a Phase 2 trial, 12-week duration might be sufficient, however, Phase 3 trials should have a duration of 6 months, as in our study. (81)

Furthermore, there is also the question of stability of negative symptoms. That can be either assessed retro- or prospectively. The recommendation is fully in line with our study design: reliable retrospective information should be available about the stability of the patient, which should be confirmed prospectively for at least 4 weeks.

5.2. Pseudospecificity

One of the biggest issues with clinical trials assessing negative symptoms is handling the question of pseudospecificity. (88)

Negative symptoms of schizophrenia can be either primary to the illness, or secondary due to other external or internal factors. (89–92) The most important factors that need to be investigated to rule out secondary symptoms are positive symptoms, depression, and EPS side effects.

It has been widely observed that when acute exacerbation of schizophrenia is treated with antipsychotics, and the positive (psychotic) symptoms improve, in parallel the negative symptoms also improve. The reason for that is the fact that when patients are experiencing psychotic symptoms such as hallucinations or delusions, they might also show less of

“normal behavior”, resulting in an increase in certain negative symptoms (e.g. avolition, anhedonia, social withdrawal).

Similarly, patients experiencing depressive symptoms can easily be mistaken for negative symptoms, resulting again in an increase in secondary negative symptoms. (89–92)

The last factor that needs to be addressed are the extrapyramidal side effects. Parkinsonian symptoms such as rigidity, bradykinesia or changes in speech can be mistaken for or directly increase negative symptoms such as for alogia, social withdrawal, or affective flattening. (89–92)

In study RGH-188-005, all of these factors have been carefully considered both during the selection of the patients with appropriate inclusion and exclusion criteria (see Section 3.2), as well as during the assessment of the study results (see Section 4.5).

Defining pre-hoc efficacy and safety analyses to appropriately evaluate study results (especially for pseudospecificity) was a crucial goal for me. Once the blind is broken, any subsequent analyses would be considered post-hoc, rendering their relevance less reliable. In total, 289 tables, 48 figures, and 57 listings were defined for the study report pre-hoc.

Patients have been selected into the study who showed significant negative symptoms (PANSS-FSNS ≥24), low positive symptoms (PANSS-FSPS≤19) at screening and at baseline, as well as they were stable in their overall symptomatology in the previous 6 months prior to screening. Furthermore, patients were excluded with significant depressive and extrapyramidal symptoms.

If we look at the results, both positive symptoms measured by the PANSS FSPS as well as the depressive symptoms assessed on the CDSS did not show relevant changes or separation throughout the 6-month study duration.

Although one of the most common adverse event was akathisia, the scales assessing the EPS symptoms did not show any trends in either of the study arms that would have signaled a secondary improvement in negative symptoms (see Section 4.6.1).

5.3. Limitations

One of the limitations of the study was the lack of placebo arm. Due to the length of the trial and the monotherapy approach, adding a placebo arm was not possible. The risk of relapse would have been significant on the placebo arm with a study duration of 6 months, while using an add-on approach would have unnecessarily increased the number and severity of the side effects. Although we cannot rule out that risperidone also had an effect

on the negative symptoms, the superiority of cariprazine over risperidone underlines the clinical effectiveness of cariprazine in negative symptoms.

Another limitation was the selection of the active comparator. While risperidone is a highly potent atypical antipsychotic, the mechanism of action of aripiprazole is closer to cariprazine, which would have made aripiprazole the logical choice as a comparator. However, based on the meta-analysis by Leucht et al., aripiprazole did not prove to be more effective in negative symptoms versus first-generation antipsychotics. (60) This was reconfirmed in our own post-hoc analyses (see Section 1.7), where aripiprazole proved to be the least effective in the treatment of negative symptoms, making the results of a theoretical Phase 3 aripiprazole-controlled trial questionable.

One alternative could have been amisulpride, as it is the only antipsychotic with the approved for "the treatment of acute and chronic schizophrenic disorders, in which […] negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterized by predominant negative symptoms". (93) However, the data generated with amisulpride in negative symptoms of schizophrenia are ambiguous. Based on the meta-analysis by Leucht et al. the effectiveness of amisulpride, risperidone, olanzapine, and clozapine are comparable. In a 6-month study assessing the effect of amisulpride and olanzapine versus placebo in patients with predominant negative symptoms showed that in such a clinical setting olanzapine proved to be the only one effective in terms of negative symptoms. (94) Furthermore, amisulpride has higher sedation rates when compared to cariprazine and the dosing regimen for positive symptoms (400-800 mg daily) differs from recommended dose range for negative symptoms (50-300 mg), making the dosing too complex for a standardized clinical trial. Retrospectively, the choice of risperidone proved to be the right one as dose ranges and expected side effect profiles were comparable and a recent metanalysis showed that no antipsychotic had any effect on primary negative symptoms other than cariprazine when compared to another antipsychotic. (84)

Further limitation is the dosing scheme and the generalizability of the study results to the approved dose range of 1.5-6 mg daily. The current study applied a target dose of 4.5 mg, with some limited possibilities to increase to 6 mg or decrease to 3 mg daily. However, 94.6% of patients were taking 4.5 mg daily as a modal daily dose.

The limitations on the clinical relevance of the results have been discussed in Section 5.

5.4. Implications and Extrapolation to Other Subpopulations

As discussed in Section 1.1, although the onset of schizophrenia is usually between the age of 18 and 35, there are cases when the diagnosis is made earlier (early onset schizophrenia) or later (late onset schizophrenia). (5,7) The current study enrolled patients between the age of 18 to 65, and the majority of the patients were in their late thirties, early forties, excluding the adolescent population and having only limited data in the older patient population.

Nevertheless, negative symptoms play an important role in the prodromal, as well as during the chronic phase of the disease. (27)

Negative symptoms appear in 73% of all cases in the prodromal phase, even before the onset of psychotic symptoms. (95) Furthermore, individuals who develop psychosis experience more severe and persistent negative symptoms during the prodromal phase. (96) During the course of the disease, while positive symptoms fluctuate and decrease in the chronic phase, negative symptoms remain persistent, even increase over time. (86)

Therefore, the efficacy of an antipsychotic on negative symptoms is relevant for not only the adult population, but also for adolescents and elderly.

Data assessing the efficacy and safety of antipsychotic medication in adolescents and elderly is scarce, however, antipsychotics are widely used in these populations as well. Although previous data suggested that efficacy may be reduced and more safety concerns might arise with antipsychotics in adolescents, a recently published paper found an exposure-response relationship regarding the efficacy in the acute phase of schizophrenia between adults and adolescents. (97–100) The relevance of this finding was also confirmed by the FDA when a general advice letter was issued to support extrapolation of efficacy of antipsychotics from adults to adolescents in schizophrenia and bipolar I disorder. (101) Safety should still be assessed in the pediatric population separately. (102)

However, with cariprazine, there are already safety data available both in the adolescent (13-17 years) and elderly (≥65 years) populations. (103)

In the adolescent population, a Phase 1 open-label clinical trial (EudraCT Number: 2016-002327-29) was conducted to assess the pharmacokinetic properties, as well as the safety and tolerability of cariprazine in patients with schizophrenia between the age range of 13-17 years. (104) The examined doses were within the approved dose range for adults (1.5-6.0 mg daily). Due to the long half-life of cariprazine and its active metabolites, the study duration was 28 days to reach steady state. To be able to compare directly pharmacokinetic and safety data between age groups, an adult group was also introduced to the study. 22 patients were enrolled in the younger pediatric age group (13- <15 years), 21 in the older pediatric age group (15- <18 years), and 20 in the adult group (18-40 years). The most frequently reported TEAEs in all age groups were somnolence and sedation, with almost all TEAEs being mild to moderate in intensity. Vital signs, clinical laboratory and ECG readouts did not reveal any clinically significant changes. Treatment-emergent Parkinsonism measured by the SAS was not present in any of the treatment groups, while treatment-emergent akathisia was observed in only one age group (15- <18 years) but without dose-relationship.

In conclusion, cariprazine was safe and well-tolerated in the pediatric population, with similar safety profile compared to adults, without showing a trend for reduced tolerability with the younger age population or higher doses. Further studies are ongoing to assess the efficacy and safety of cariprazine in this patient population.

The study assessing the long-term safety, tolerability, and efficacy of cariprazine in the elderly population was conducted in Japan (ClinicalTrials.gov study code: NCT01625897). (105) The study was a 48-week long, open-label clinical trial with 2 active treatment arms (cariprazine and risperidone). Due to the long-term treatment, the dosing was flexible for both treatment arms, ranging between 1.5-9.0 mg daily for cariprazine and 2.0-12.0 mg daily for risperidone. Altogether there were 125 patients randomized, 27 patients met the criterion of elderly (≥65 years), out of which 17 patients received cariprazine and 10 risperidone. During the course of the study, in the elderly group all patients experienced at least one TEAE, with the exception of one patient. The most common adverse events reported in the cariprazine group were schizophrenia, nasopharyngitis, insomnia, hypertension and weight increased, while in the risperidone group hyperprolactinemia, insomnia and Parkinsonism. There were no clear and clinically significant changes observed in terms of clinical laboratory parameters, vital signs or

ECG. More patients experienced treatment-emergent Parkinsonism in the risperidone group (40%) than in the cariprazine group (17.6%).

In conclusion, although data are limited in both adolescents and elderly, cariprazine seems to be safe and well-tolerated in these patient populations as well, showing a safety profile similar as of adults, offering a potential treatment option for two populations who predominantly suffer from negative symptoms of schizophrenia.

6. CONCLUSIONS

In conclusion, cariprazine proved to be effective in the treatment of primary, predominant negative symptoms. I was able to verify that the carefully defined inclusion and exclusion criteria ensured an appropriate patient population for assessing an antipsychotic's efficacy on primary negative symptoms. Furthermore, the selected primary endpoint proved to be suitable to demonstrate efficacy on primary negative symptoms: the change from baseline to end on the PANSS-FSNS showed statistically significant difference in the favor of cariprazine over risperidone. Patient functionality, measured as a secondary endpoint on the PSP, also showed statistically significant difference between the two treatment arms. This indicates that the improvement in symptomatology translated into meaningful functional improvements. With the well-defined analyses I was able to demonstrate consistent and robust data throughout the various endpoints:

- negative symptom improvement was followed by improvement in functionality
- all relevant subdomains of functionality showed similar results
- the improvements seen in the overall condition of the patients – measured by the Clinical Global Impressions scales – were consistent with the improvements in symptomatology and functioning
- positive and depressive symptoms measured by the PANSS-FSPS and CDSS, respectively, did not improve during the study, excluding the possibility of a secondary improvement in negative symptoms
- extrapyramidal symptoms, measured by the BARS, AIMS, and SAS, did not show any signals that would raise concerns about pseudospecificity.

The study design and the careful patient selection ensured that the results are relevant and can be generalized to primary negative symptoms in patients with predominant negative symptoms. Furthermore, based on preliminary safety results, cariprazine might offer a safe and effective treatment option for adolescents and elderly, who primarily suffer from predominant negative symptoms. Hence, although the exact pathophysiology of negative symptoms is still unknown, I was able to provide first time evidence in a clinical setting that D3 receptors might play an important role in the negative symptomatology and so providing the first effective treatment for patient suffering from negative symptoms.

7. SUMMARY

INTRODUCTION: The dopaminergic system plays a crucial role in many neuropsychiatric disorders. One of the mostly investigated conditions is schizophrenia. While it is a widely accepted hypothesis that D2-antagonism is necessary to achieve effectiveness in the positive symptoms of schizophrenia, the pathophysiology of negative symptoms is less known. The D2 mechanism was confirmed by many effective typical and atypical antipsychotics, all primarily targeting the D2 receptors, there has been no drug yet that would have had a relevant in vivo affinity towards the D3 receptors. The effect of cariprazine had been proved on the positive symptoms of schizophrenia, then assessed on the negative symptoms in post-hoc analyses based these short-term placebo- and active-controlled schizophrenia trials.

OBJECTIVE: The objective was to assess the effectiveness of a novel D3 preferring D3/D2 partial agonist, cariprazine, on the negative symptoms of schizophrenia, providing additional evidence to support the D3 hypothesis.

METHODS: Based on the promising post-hoc data, a randomized, double-blind, active-controlled Phase IIIb study was initiated specifically assessing the efficacy of cariprazine in patient with predominant negative symptoms. The study duration was 6 months, with an active comparator of risperidone. The primary endpoint was based on the PANSS Factor Score for Negative Symptoms, the secondary endpoint was assessing patient functionality using the Personal and Social Performance scale.

RESULTS: Cariprazine proved to be statistically significantly superior both on the primary and secondary endpoints compared to risperidone. The results were also confirmed by the global scales (Clinical Global Impression – Severity/Improvement). There have been no factors identified related to pseudospecificity that would have affected the results.

CONCLUSION: Cariprazine proved to be safe and effective in the treatment of primary negative symptoms in patients with predominant negative symptoms of schizophrenia, providing additional proof that the D3 receptors might play a crucial role in the negative symptomatology.

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