18 May 2017
EMA/CHMP/353055/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Reagila

International non-proprietary name: cariprazine

Procedure No. EMEA/H/C/002770/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

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ADO adverse event associated with drop out (premature study discontinuation)

AE adverse event

AIMS Abnormal Involuntary Movement Scale

ALP alkaline phosphatase

ALT alanine aminotransferase (same as serum glutamic-pyruvic transaminase [SGPT])

AST aspartate aminotransferase (same as serum glutamic-oxaloacetic transaminase [SGOT])

AUC area under the concentration-time curve

BARS Barnes Akathisia Rating Scale

BCVA best-corrected visual acuity

BD bipolar depression

BMI body mass index

BP blood pressure

bpm beats per minute

BUN blood urea nitrogen

CDR cognitive drug research system attention battery

CFB change from baseline

CI confidence interval

CGI-S Clinical Global Impressions–Severity

CGI–I Clinical Global Impressions –Intensity

CQA Critical Quality Attribute

Cmax maximum concentration

CNS central nerve system

CPK creatine phosphokinase

CK-MB creatine kinase MB isoenzyme

C-SSRS Columbia–Suicide Severity Rating Scale

CSR Clinical Study Report

CTT color trails test

CU Content Uniformity

CYP cytochrome P450

DAD Diode-Array Detector

DB double-blind

DBP diastolic blood pressure

DCAR desmethyl cariprazine

DDCAR didesmethyl cariprazine

DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision

DVT deep vein thrombosis

ECG electrocardiogram, electrocardiographic

EEG electroencephalogram

EPS extrapyramidal symptom

ERG electroretinogram

FDA US Food and Drug Administration

GCP Good Clinical Practice

GERD gastroesophageal reflux disease

GGT gamma-glutamyl transferase

HCG human chorionic gonadotropin

HDL high-density lipoprotein

ICH International Conference on Harmonisation

IOP intraocular pressure

IP investigational product

IV intravenous

LD Laser Diffraction

LDH lactate dehydrogenase

LDL low-density lipoprotein

LFT liver function test

LLN lower limit of normal

LOCS III Lens Opacities Classification System III

MAA Marketing Authorization Application

MDD major depressive disorder

MedDRA Medical Dictionary for Regulatory Activities

MRHD maximum recommended human dose

MTD maximum tolerated dose

MTPC Mitsubitshi Tanabe Pharma Corporation

NC nuclear color

NDA New Drug Application

NEAE newly emergent adverse event

NMS neuroleptic malignant syndrome

NO nuclear opalescence

NOEL no-observed-effect level

OCT ocular coherence tomography

OL open label, OLP open label period

QD every day

QTc QT interval corrected for heart rate

QTcB QT interval corrected for heart rate using the Bazett formula (QTcB = QT/(RR)½)

QTcF QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓)

QTcNi QT interval corrected for heart rate using an individual correction;

PANSS Positive and Negative Syndrome Scale

PCS potentially clinically significant

PD pharmacodynamic

PE pulmonary embolism

Ph.Eur. European Pharmacopoeia

PID patient identification number

PK pharmacokinetic

PK/PD pharmacokinetic/pharmacodynamic

PMDA Pharmaceuticals and Medical Devices Agency (Japan)

PSC posterior subcapsular cataract

PT preferred term (referring to adverse event coding using MedDRA)

QbD Quality by design

QC Quality Control

QTPP Quality target product profile

RIP run-in phase

SAE serious adverse event

SAS Simpson-Angus Scale

SBP systolic blood pressure

SD standard deviation

SDS Sheehan Disability Scale

SMQ standardized MedDRA query

SmPC Summary of products characteristics

SOC system organ class

SP stabilization phase

TEAE treatment-emergent adverse event

TIA transient ischemic attack

TSH thyroid-stimulating hormone

ULN upper limit of normal

US United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gedeon Richter Plc. submitted on 2 March 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Reagila, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 June 2012.

The applicant initially applied for the following indication:

Treatment of schizophrenia in adult patients. Treatment of schizophrenia with predominant negative symptoms in adult patients.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that cariprazine was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0076/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0076/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance cariprazine contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Outi Mäki-Ikola

- The application was received by the EMA on 2 March 2016.
- The procedure started on 24 March 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 June 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 June 2016.
- During the meeting on 7 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 8 July 2016.
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP and PRAC members on 31 January 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 10 February 2017.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 13 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP and PRAC members on 3 May 2017.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP and PRAC members on 12 May 2017.
- During the meeting on 18 May 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Reagila.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Schizophrenia is a life-long psychiatric disorder. The cardinal symptoms fall into 3 domains: positive symptoms such as delusions and hallucination, negative symptoms such as lack of drive and social withdrawal, and cognitive symptoms such as problems with attention and memory.

2.1.2. Epidemiology

Schizophrenia typically begins in late adolescence or early adulthood. Its lifetime prevalence is about 1 % globally. It is equally prevalent in men and women and affects more than 21 million people worldwide. Incidence rates per year of schizophrenia in adults within a quite narrow range between 0.1 and 0.4 per 1000 population (WHO).

2.1.3. Biologic features

Dopamine hypothesis as simplified posits that schizophrenia results from too much dopaminergic activity. Efficacy of antipsychotic medications correlates with their ability to antagonize dopamine type 2 (D2) receptors. In addition, several other neurotransmitters and receptor types are involved.

An enlargement of cerebral ventricles, reduced brain symmetry, deficits in prefrontal cortex and decrease in size of hippocampus and amygdala have been all observed in patients with schizophrenia.

2.1.4. Clinical presentation

A patient usually gradually recovers from the first episode of schizophrenia. However, relapses are common, and pattern of the illness during the first 5 years indicates generally the course. In general, deterioration in the patient's baseline functioning happens after each relapse. Positive symptoms tend to ease with time, but the socially debilitating negative and deficit symptoms may increase and become more severe. Only 10-20% of schizophrenia patients have been described to achieve a good outcome. It has been estimated that 20-30% continue to experience moderate symptoms and 40-60% remain significantly impaired. This means that patients with schizophrenia often have great difficulties in integrating in society and to normal life, for example through the loss of an acquired capability to earn a livelihood or the disruption of studies. In addition, comorbidity with other somatic diseases, such as obesity, cardiovascular diseases and diabetes mellitus, as well as with substance abuse is common. People with schizophrenia have a 40-60% higher rate of dying prematurely than general population due to physical health problems and suicide.

2.1.5. Management

Antipsychotic medications are the mainstay treatment for schizophrenia in addition to psychosocial interventions. Antipsychotics diminish symptoms and reduce relapse rates. Antipsychotics have a wide variety of pharmacological properties but all have a capacity to antagonize postsynaptic dopamine receptors in the brain.

Acute psychotic symptoms require immediate attention and focuses to alleviating of severe symptoms with an adequate trial of medication. If no adequate response is followed by a few weeks trial, treatment should be changed to another type of antipsychotic. Side effects are very common with antipsychotics.

These include extrapyramidal side effects, tardive dyskinesia, sexual side effects, sedation, just a few to mention.

2.2. About the product

Cariprazine (RGH-188) is a novel atypical antipsychotic, an orally active and potent dopamine D2 and D3 receptor partial agonist with preferential binding to D3 receptors and partial agonist at serotonin 5-HT1A receptors.

Reagila (cariprazine) is intended for the treatment of schizophrenia in adult patients. The Applicant proposed once daily doses 1.5-6 mg. Treatment should be initiated with 1.5 mg dose and increased with 1.5 to 3 mg increments to clinically justified target dose. Maximum daily dose is 6 mg.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as hard capsules containing cariprazine hydrochloride corresponding to 1.5, 3, 4.5 and 6 mg of cariprazine as active substance.

Other ingredients are:

Capsule content: pregelatinized (maize) starch, magnesium stearate.

Capsule shell (1.5 mg capsule): titanium dioxide (E 171), gelatin.

Capsule shell (3 mg capsule): allura red AC (E 129), brilliant blue FCF (E 133), titanium dioxide (E 171), yellow iron oxide (E 172), gelatin.

Capsule shell (4.5 mg capsule): allura red AC (E 129), brilliant blue FCF (E 133), titanium dioxide (E 171), yellow iron oxide (E 172), gelatin.

Capsule shell (6 mg capsule): brilliant blue FCF (E 133), allura red AC (E 129), titanium dioxide (E 171), gelatin.

Printing ink (black: 1.5 mg, 3 mg and 6 mg capsules): shellac, black iron oxide (E 172), propylene glycol, potassium hydroxide

Printing ink (white: 4.5 mg capsule): shellac, titanium dioxide (E 171), propylene glycol, simeticone.

The product is available in transparent hard PVC/PE/PVDC blister heat-sealed with hard aluminium foil backing as described in section 6.5 of the SmPC.

2.3.2. Active Substance

General information

The chemical name of cariprazine is *trans*-*N*-{4-[2-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-*N*',*N*'-dimethylurea corresponding to the molecular formula $C_{21}H_{32}Cl_2N_4O$. It has a relative molecular mass of 427.41 g/mol and the following structure:

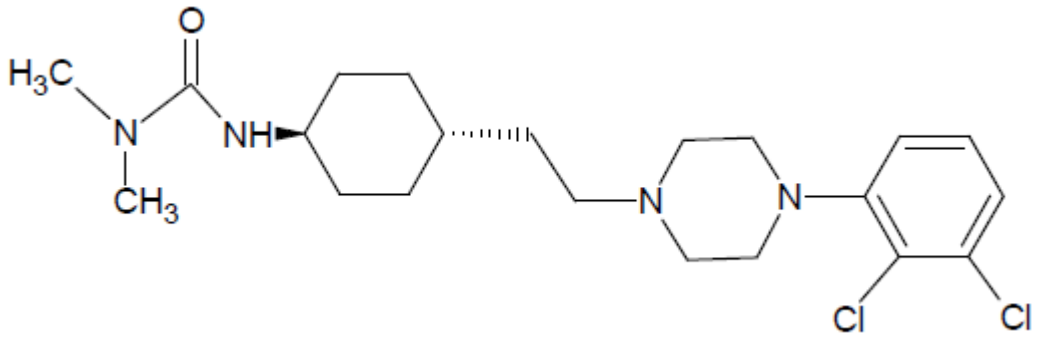


Figure 1 – Structure of cariprazine

The confirmation of the chemical structure has been conducted based on UV, IR, ^{1}H-NMR, ^{13}C-NMR and ESI mass spectra.

The active substance is a white or almost white crystalline powder, non-hygroscopic, freely soluble in methanol, slightly soluble in dichloromethane and, ethanol, very slightly soluble in acetone, acetonitrile and water, and practically insoluble in isopropanol and *N*,*N*-dimethylformamide.

Cariprazine has a non-chiral molecular structure. Polymorphism has been observed for the active substance, Form I polymorph is the thermodynamically most stable solid form and it was identified by XRPD and IR. Form I is also physically stable under stability storage conditions.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The synthesis of the active substance is described in five stages, which comprise three synthetic steps, one de-protection and one purification step using commercially available well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance packaging complies with the EC 10/2011 as amended.

Specification

The active substance specification includes tests for: characters (visual), particle size distribution (LD), identification active substance (IR, HPLC), identification chloride (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash/residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), metal residue (ICP), related substances (HPLC, LC), residual solvents (GC), microbiological purity (Ph. Eur.), and assay (HPLC).

Limits for potentially genotoxic impurities have been set in line with ICH M7.
The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (5 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 10 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch.

Results under stressed conditions: alkaline treatment (0.2 N NaOH:ACN = 3:7 at 80 °C), acidic treatment (0.1N HCl:ACN = 9:1 at 80 °C), peroxidic treatment (3% H_2O_2:ACN = 1:1 at room temperature), and treatment in solid state were also provided for one batch.

The following parameters were tested*:* characters, loss on drying, related substances, and assay. Supplementary tests as microbiological purity and polymorphic testing are performed at the start and after 60 months (long-term conditions). The analytical methods used were the same as for release and are stability indicating.

Under accelerated and long term conditions, all tested parameters were within the specifications for the primary and supportive stability batches.

Regarding the photostability testing, the active substance does not decompose due to the effect of light.

The stability results indicate that the active substance manufactured by the proposed suppliers sufficiently stable. The stability results justify the proposed retest period of 60 months without special storage conditions in the proposed container.

2.3.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented in size 4 (1.5 mg, 3 mg, and 4.5 mg) or size 3 (6 mg) hard capsules filled with a white to yellowish white powder mixture.

The proposed specification for particle size distribution was based on batch data the active substance. Dissolution test results justify the final particle size limits for cariprazine hydrochloride.

The compatibility between the active substance and the excipients of the capsule fill (pregelatinised maize starch and magnesium stearate) was demonstrated under long term (4 weeks at room temperature), accelerated (4 weeks at 40 °C) and stressed conditions (4 weeks at 50 °C). A similar study of the active substance mixed with milled capsule shells of all colour versions under long term and stressed conditions confirmed compatibility with the capsule shells.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except for the colourants. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.3.1 of this report.

A quality-by-design (QbD) approach was used for the formulation development. Key attributes of the quality target product profile (QTPP) which formed the basis of design at the early stage of product development were defined as: indication, route of administration, dosage form, strengths, stability, container closure and finished product quality attributes

Based on the QTTP, the following initial critical quality attributes (CQA) were established: identification, assay, uniformity of dosage units, degradation products, dissolution and microbiology.
Dissolution profiles using the quality control (QC) method were generated to characterise the effect on capsule dissolution of the following variables: diluent used in the formulation blend; particle size distribution of the active substance; diluent compaction of the formulation blend.

The capsule shells used throughout the development of the finished product and commercial manufacture have been assessed for product performance by *in vitro* dissolution tests and demonstrated to have no impact on the release characteristics of the finished product.

A quality-by-design (QbD) approach was used during the development of the manufacturing process for the finished product. The strategy for manufacturing process development was based on following key steps:

1. Acquire process understanding of the finished product.

2. Risk assessment and prior knowledge were used to identify material attributes and process parameters for each step with a high risk of impacting the finished product critical quality attributes (CQAs) and these were regularly re-evaluated during development.

The primary packaging is PVC/PE/PVDC blister heat-sealed with hard aluminum foil backing. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: screening, blending, final blending, encapsulation and primary packaging. The process is considered to be a standard manufacturing process.

The in-process controls are adequate for controlling these steps.

Major steps of the manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: characters (visual), uniformity of mass (capsule filling) (Ph. Eur.), identification (HPLC, DAD), colorant in the capsule shell (colour reaction), related substances (HPLC), microbiological purity (Ph. Eur.), assay (HPLC), dissolution (Ph. Eur.), and uniformity of dosage units (Ph. Eur. / HPLC).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from all strengths of the finished product stored under long term conditions for 60 months at 25 ºC / 60% RH, under intermediate conditions for 60 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in

the primary packaging proposed for marketing. A reduced stability testing, matrixing design was followed according to the recommendations outlined in ICH Q1D.

Samples were tested for characters, uniformity of mass (filling mass), assay, tests for purity (related substances and microbiological purity), and dissolution. The analytical procedures used are stability indicating.

All results comply with the proposed specification.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It was concluded that the capsules should be stored protected from light.

Based on available stability data, the proposed shelf-life of 60 months keeping the blister in the outer carton in order to protect from light as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. A valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product. However, no design spaces were claimed for the manufacturing process of the finished product.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

Not applicable

2.4. Non-clinical aspects

2.4.1. Introduction

The standard battery of the pharmacology and toxicology studies were completed and submitted.
All pivotal toxicity studies, including the safety pharmacology studies were performed in accordance with GLP principles, as declared by the applicant.

2.4.2. Pharmacology

Primary pharmacodynamic studies

Cariprazine is a dopamine D2/D3 receptor and serotonin 5-HT1A receptor partial agonist and a 5-HT2 receptor antagonist. Functionally, cariprazine has shown both agonist and antagonist properties at the dopamine D2/D3 receptor depending on the test conditions, which overall fits a partial agonist pharmacologic profile. The major human active metabolites, DDCAR and DCAR, have a pharmacodynamic profile comparable to that of the parent compound, but DDCAR displays greater antagonistic effect on both D3 and D2 receptors.

Receptor binding data and results from functional assays showed that CAR and its major active human metabolites DCAR and DDCAR have assay-dependent dopamine D2 and D3 receptor antagonist-partial agonist-full agonist or 5-HT1A partial agonist profile, and antagonist profile at serotonin 5-HT2B receptors, whereas Risperidone showed consistent antagonist profile at dopamine D2 and D3 receptors. Moreover, the results from the animal models representative for negative symptoms indicate favourable effect of CAR in these models.

In vitro

Cariprazine has high affinity for human recombinant dopamine D3 receptors (Ki = 0.085 nM) and high (but 6-8 times lower relative to D3 receptor) affinity for dopamine D2 receptors (Ki = 0.49 and 0.69 nM for D2L and D2S, respectively) and serotonin 5-HT2B (Ki =0.58 nM) and 5-HT1A (Ki =2.6 nM) receptors. Cariprazine shows moderate affinity for σ1, 5-HT2A, and H1 receptors (Ki values: 18.3 nM, 18.8 nM, and 23.2 nM, respectively). In general, the in vitro human receptor binding profiles of the two major active metabolites of cariprazine, DCAR (D3, Ki = 0.057 nM; D2, Ki = 1.41 and 2.64 nM for D2L and D2S, respectively, 5-HT2B, (Ki =0.53 nM) and 5-HT1A, (Ki =1.7 nM) and DDCAR (D3, Ki = 0.038 nM; D2, Ki = 0.81 and 1.31 nM for D2L and D2S, respectively, 5-HT2B, (Ki =0.47 nM) and 5-HT1A, (Ki =2.93 nM) are comparable to the parent compound, but some variation was seen in the binding preference results at D3 over D2 receptor between cariprazine and DDCAR. Further, the DDCAR, being a major and long lasting metabolite in humans was less potent (3-10–fold) than cariprazine under the in vivo conditions tested and showed some minor differences in its agonist efficacy at D2 and 5-HT1A receptors.

In cell based functional assays, cariprazine, DCAR and DDCAR demonstrated assay dependent partial agonism with varying potency and intrinsic activity at different signalling mechanisms coupled to D_2 or D_3 receptors).

In a broad target selectivity screen, cariprazine and the metabolites DDCAR and DCAR did not exhibit appreciable binding affinity (IC_{50} > 1 μM) for any of the 71 receptors, transporters, or ion channels tested.

In vivo

In neurochemical studies, similar to other dopamine D2 receptor antagonists, cariprazine increased the dopamine turnover (DOPAC+HVA)/DA ratio) in rodent brain region such as striatum and frontal cortex. Moreover, consistent with in vitro data, cariprazine acts as a partial agonist when the dopaminergic tone is low (in reserpine model) but shows antagonist activity when the dopamine tone is high (antagonism of effect of apomorphine in the GBL model).

Receptor occupancy studies in rat in vivo show that acutely administered oral doses of cariprazine (within the antipsychotic-like effective range ≥ 0.3 mg/kg PO) occupy D3 (ED50 ~ 0.4 mg/kg) and D2 receptors (ED50 ~ 0.4 mg/kg) to a similar extent.

Electrophysiology studies in vivo show that chronic oral administration of cariprazine (0.1, 0.3 and 1 mg/kg, PO for 21 days) dose-dependently reduced dopamine neuronal firing with limbic (VTA) vs. striatal selectivity (-45%, -59% and -66% inhibition), similar to the effect reported for aripiprazole.

The antipsychotic-like activity of cariprazine and DDCAR was evaluated in standard behavioural models detecting antagonist activity at D2 receptor (e.g. apomorphine- and amphetamine-induced hyper-locomotion). Efficacy in these in vivo disease-like models was commonly observed in the dose range 0.1-1 mg/kg, PO (predicted Cmax = 10-100 ng/mL; e.g. ED50 values 0.27 - 0.31 mg/kg at 1 and 4h post-dose in the apomorphine-induced climbing model, respectively).

Cariprazine also reversed cognitive- and social deficits (effective dose-range: 0.02-0.25 mg/kg, IP or PO) in rodent models of schizophrenia induced by NMDA antagonists (e.g. PCP) and demonstrates antidepressant-like properties (effective dose- range: 0.03-0.25 mg/kg, IP) in animal models of anhedonia (chronic mild or unpredictable stress), which may in turn indicate effects of cariprazine on negative symptoms of schizophrenia.

In general, the in vivo pharmacological profile of the metabolite DDCAR was comparable to cariprazine, although it displays a lower potency (2-10-fold depending on the assay).

Secondary pharmacodynamic studies

Secondary pharmacodynamics studies were conducted to demonstrate effects of cariprazine at other indications. Anxiolytic efficacy was shown in the rat Vogel test (doses of 0.2-1.6 mg/kg PO), which is in the range of its antipsychotic-like effect and cariprazine reduces the reward value in cocaine self-administration model.

Safety pharmacology programme

CNS

In CNS safety studies in rodents, a single oral dose of cariprazine resulted in several observations in the Irwin screen that may be related to the pharmacology of the drug including decreases in body temperature, muscle tone, grip strength, startle response, body tone, and locomotion, as well as abnormal gait and impaired motor coordination. These effects were noted within the pharmacologically-effective dose-range of > 0.4 mg/kg (estimated C_{max} ~ 14 ng/ml). Based on these results, the exposure margin for CNS effects in rats, relative to the C_{max} (~ 23 ng/mL) at the MRHD of 6 mg/day was < 1.

Cariprazine produced no catalepsy in rats at doses ≥ 85 mg/kg (HED= 822 mg; exposure margin of 140 at the MRHD of 6 mg/day) or at least 100-fold the ED50 value of its antipsychotic-like efficacy. Moreover, cariprazine inhibited haloperidol (3 mg/kg IP)-induced catalepsy yielding a minimum effective dose of 2 mg/kg PO. In contrast to these preclinical data, extrapyramidal symptoms (EPS) were frequently seen in the clinical studies.

Cariprazine did not exhibit pro-convulsant or anticonvulsant activity in the PTZ seizure test in Wistar rats (up to 2.5 mg/kg PO (HED= 24 mg); exposure margin of 4 at the MRHD of 6 mg/day) nor did cariprazine potentiate the hexobarbital-induced sleep time in mice.

Cardiovascular

Cariprazine showed a concentration-dependent inhibition of the human Ether-a-go-go related gene (hERG) channel maximum tail current amplitude in vitro, with an estimated IC50 range of 3-4 µM. The exposure margin for hERG activity is estimated to ~ 55-75-fold over the Cmax (~ 23 ng/mL [~ 54 nM] at the MRHD of 6 mg/day). Similar to cariprazine, DCAR and DDCAR blocked hERG

channel-mediated currents in a non-GLP study in vitro, with estimated IC_{50} values for DCAR (3.6 µM) and DDCAR (3.5 µM), respectively.

In telemetry studies in conscious dogs, cariprazine at a dose of 3.0 mg/kg PO (Cmax= 383 ng/mL; exposure margin of ~16 relative to the Cmax (~23 ng/mL) at the MRHD of 6 mg/day) produced a significant increase (~ 40-50%) in heart rate at 4 and 6 hours post-dose, whereas it caused little or no reduction in blood pressure. Cariprazine tested up to 3 mg/kg PO had no biologically significant effects on PR and QRS intervals of the ECG and did not prolong the QT or QTc intervals. No arrhythmia or other changes in the morphology of the ECG were observed in the dogs.

Gastrointestinal system, renal and respiratory function

Cariprazine, tested at the highest dose of 2.5 mg/kg PO (HED= 24 mg; exposure margin of 4 based on the MRHD of 6 mg/day) had no effects on gastric motility or secretion and did not induce ulcerogenic activity in male rats. Cariprazine, tested at the highest dose of 2.5 mg/kg PO (HED= 24 mg; exposure margin of 4 based on the MRHD of 6 mg/day) had no significant effect on diuresis and urinary electrolyte excretion in rats. Cariprazine (0.5, 2.5, 12.5 mg/kg, PO) decreased the respiration rate significantly in rats at all doses (maximum decrease ~ 43% at 12.5 mg/kg), with a compensatory increase in tidal volume at all doses. This effect was different from that of the respiratory depressant effects of morphine which decrease both respiratory rate and tidal volume. Thus, cariprazine was not considered to induce major respiratory depression effects.

Endocrine function

Cariprazine at 0.5 mg/kg (HED = 0.08 mg/kg or 4.8 mg) and higher induces hyperprolactinemia in both rat in both sexes, and increases in serum prolactin levels in the female animals were higher than those in the males. The exposure margin for prolactin effects in rats, relative to the MRHD of 6 mg was <1. Noteworthy, the induced hyperprolactinemia was lower for cariprazine compared to risperidone during short-term clinical studies.

DCAR and DDCAR metabolites

The major metabolites of cariprazine, in particular DDCAR, show relatively high and long-lasting plasma concentration in humans. Based on toxicokinetic data obtained in the toxicology study package of cariprazine, DCAR is considered as completely characterised in the safety pharmacology program. DDCAR can be considered also appropriately characterised in terms of cardiovascular safety but not in terms of the other organ systems studied only in rodents because the plasma concentration of DDCAR is rather low at the safety pharmacology dose range applied in rats and mice. Thus, DDCAR appeared to have been incompletely characterised in the safety pharmacology program since in *vivo* safety data for some organ systems are lacking. However, given the stage of the clinical development, further *in vivo* study with these metabolites is not likely to yield data relevant for human risk assessment.

2.4.3. Pharmacokinetics

Absorption

Cariprazine is a lipophilic compound (Mw 427.41), with low pH-dependent solubility (BCS class 2) and high permeability. The single oral dose studies indicate rapid absorption in mouse, rat and dog with Cmax generally observed after 0.5-1 h in rodents, 1-2 h in dogs and ~ 2 h in monkey. The IV pharmacokinetics was characterized by plasma clearance values in rat of 26-32 mL/min.kg and with lower values in dog (~ 15 mL/min.kg). The apparent elimination half-life ranged from 2 - 3 hrs in rat, 3 – 6 hrs in monkey and 4 - 7 hrs in dog, with no obvious difference between the two genders. The absolute oral bioavailability was

52-63% in rats and ~ 64-80% dogs, indicating incomplete absorption and some first-pass effect. Co-administration with food had limited effects on cariprazine exposure and PK parameters in dogs.

Plasma concentrations of the two major human active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), were measured in rats and dogs following a single oral dose. Similar to cariprazine, the plasma concentration of DCAR reached a maximum at 1-2 hours in both species, whereas the Tmax of DDCAR was greater than that of cariprazine (6 hours in rats and 8-12 hours in dogs). The half-life of DCAR was similar to that of cariprazine for both species (T½ ~3 hours in rats; T½ 4-7 hours in dogs) whereas the plasma half-life (T½) of DDCAR was considerably longer than that of cariprazine for dogs (16-25 hours).

Distribution

Plasma protein binding of cariprazine was high across all preclinical species examined as well as in human (~ 96%). In human plasma, DDCAR and DCAR were bound to plasma proteins by ~ 93 % and ~ 95 %, respectively.

Studies on red blood cell binding of [14C]-cariprazine indicate that cariprazine in the blood was bound to the red blood cells in human by 30% and by approximately 45% in rats and dogs. The binding to plasma proteins and red blood cells was independent of gender and the cariprazine concentration.

Cariprazine readily crosses the blood-brain barrier after oral administration in rats (brain-to-plasma AUC ratio was ≥ 7.6-fold). Cariprazine has also large volume of distribution of up to 7.8 L/kg in the rat and 19 L/kg in the dog and distributes well to most tissues.

Quantitative whole body phosphor imaging (QWBPI) was used to determine the tissue distribution of cariprazine. Following an oral administration of [14C]-cariprazine to male and female albino rats and male and female Long Evans rats, the 14C-radioactivity was distributed into almost all tissues at 2 hr post-dose (Tmax). No obvious sex-dependent differences in tissue distribution of 14C-radioactivity were observed. Distribution of [14C]-cariprazine related radioactivity was similar in pigmented and non-pigmented rats, with the exception of the skin and choroid layer of the eyes in pigmented rats, suggesting binding to melanin-containing tissues. In pigmented rats the elimination was slow from many tissues including the adrenal cortex, Harderian gland, intraorbital lachrymal gland, liver, submaxilliary salivary gland, pigmented fur/skin, and eye choroid layer where radioactivity persisted up to 2 weeks post-dose and it persisted up to 4 weeks post-dose in adrenal cortex and liver. At 8 weeks post-dose, small amounts of radioactivity were still detected in the choroid layer of the eyes and pigmented fur/skin. In toxicology studies, including phototoxicity, cataract was observed in animals whereas this finding was not reported in clinical trials. A conventional mass balance study using [14C]- labelled cariprazine was not conducted in healthy volunteers due to safety concerns as the eyes could have been exposed to radioactivity for a long duration. Therefore, there is an incomplete understanding of possible additional circulating drug-related material in human plasma.

Following a single oral 3 mg/kg dose of [14C]-cariprazine to timed-pregnant female rats on Day 13 -18 of gestation, radioactivity, as measured by QWBA, was widely distributed to maternal tissues, crossed the placenta, and was quickly distributed to fetal tissues. At 2 h post-dosing, radioactivity concentration in fetus was approximately 1.7 times higher than that in maternal plasma. Radioactivity concentrations were still present in ovary, uterus, fetal liver, fetal kidney and fetal brain at 48 h after administration.

Metabolism

Biotransformation of cariprazine in nonclinical species was represented by liver P450 metabolism, including demethylation (desmethyl cariprazine and didesmethyl cariprazine), hydroxylation (hydroxy cariprazine) and a combination of demethylation and hydroxylation (hydroxy desmethyl cariprazine and hydroxy didesmethyl cariprazine) in rat and dog. Hydroxylated metabolites (hydroxy cariprazine and

hydroxy desmethyl cariprazine) are subsequently biotransformed to their corresponding sulfate and glucuronide conjugates. All three hydroxy metabolites were excreted mainly in feces, while the glucuronide and sulfate conjugates were excreted mainly in urine. Cariprazine was also extensively metabolized by e.g. hydroxylation and demethylation in humans and less than 5% of the dose was excreted as unchanged drug.

Among all identified metabolites, DCAR and DDCAR are considered the two major active metabolites since their steady-state AUC was >10% (40% for DCAR and 3-fold for DDCAR) of that for the parent drug.

Excretion

Cariprazine was mainly eliminated by metabolism, with only a small fraction of the dose excreted unchanged. Excretion of radioactive material following administration of oral doses of radiolabelled [14C] cariprazine was studied in rats and dogs. The radioactivity of cariprazine and its metabolites was recovered in feces and urine in both species. The primary route of elimination of cariprazine and its metabolites was biliary (approximately 77% of the dose in rats and approximately 62% of the dose in dogs) with renal excretion as a minor route (approximately 15% of the dose in rats and approximately 21% of the dose in dogs). The biliary excretion was confirmed as the primary route of elimination in bile-duct cannulated rats, where approximately 72 % of the single oral dose of [14C] cariprazine was excreted in bile.

2.4.4. Toxicology

Single dose toxicity

In mice and female rats, the minimum lethal dose after oral administration of cariprazine was 100 mg/kg, corresponding to a HED of 8.1 to 16 mg/kg. In male rats, the minimum lethal dose was approximately 200 mg/kg, corresponding to a HED of 32 mg/kg. Drug-related clinical findings preceding death in both mice and rats included lethargy, ataxia, hunched posture, decreased activity, palpebral closure and hypothermia.

Repeat dose toxicity

Cariprazine has been evaluated in repeat-dose toxicity studies in Wistar rats (up to 26 weeks with 4 weeks recovery) and in Beagle dogs (up to 52 weeks with 8 weeks recovery). To minimize signs of acute toxicity and enable adaptation, a dose-escalation period of ~2 to 4 weeks prior to administration at the final dose levels were included in most pivotal repeat-dose oral toxicity studies. The main target organs of toxicity are CNS, adrenal cortex, eye, female reproductive organs and potentially the sciatic nerve. In addition, pronounced decreases in plasma cholesterol and triglycerides levels were observed.

Pre-terminal mortalities considered as likely related to cariprazine treatment were seen in all species. In the 7-week study in Tg.rasH2 and CByB6F1 hybrid mice, one mouse given 140 mg/kg/day (cariprazine AUC ~43600 ng·h/mL) was found dead on Day 51, after displaying adverse clinical signs on Day 50. In the 4-week rat study, 1 rat was sacrificed moribund at 12.5 mg/kg/day (cariprazine AUC ~5600 ng·h/mL), and at 50 mg/kg/day (cariprazine AUC ~10500 to 28500 ng·h/mL), in total 15 rats were either found dead or sacrificed moribund. Most rats showed adverse clinical signs prior to death/sacrifice. In the 13-week dog study, one dog was found dead after 22 doses at 8 mg/kg/day (cariprazine AUC ~5700 ng·h/mL). This dog did not display adverse clinical signs and the cause of death was not revealed during necropsy. However, in the absence of an explanation for the cause of death, a relation to treatment is considered likely.

Clinical signs in the repeat-dose toxicity studies in mice, rats, and dogs were mainly neurologic in nature and included tremor, disorientation, abnormal gait, decreased motor activity, flat body posture, limb

abduction, lower lip retraction, increased or decreased muscle tone, back muscle contraction, hunched posture, lethargy, piloerection, brown/yellow fur staining, and chromodacryorrhea. The CNS signs are attributed to the exaggerated primary pharmacological activity of cariprazine and showed a dose-dependent incidence and severity. No or few clinical signs were observed in the sub-chronic studies in rats and in the chronic dog study due to adaptation. Decreases in body weight, body weight gain and food consumption were observed in many studies.

Lung findings

In rats, non-reversible alveolar macrophage foci, accompanied by alveolar inflammation, were observed in the 4-week toxicity study at dose levels above the MTD. In the 13-week toxicity study, discolored tan foci associated with an increased incidence in alveolar/intra-alveolar macrophages with foamy cytoplasm with/without inflammatory cell infiltrate/hemorrhage were observed. In the 26-week toxicity study, alveolar/intra-alveolar macrophages with foamy cytoplasm were observed in males at 10 mg/kg/day and in females at all dose levels. No reversibility was demonstrated. Lung samples of females given 12.5 mg/kg/day were further examined by EM examination, showing presence of concentric lamellar bodies within lysosomes in the cytoplasm of Type II pneumocytes or macrophages, indicating the occurrence of PLD. The NOAEL for the lung PLD is 3 mg/kg for males corresponding to 3.5-fold clinical exposure based on cariprazine AUC. A NOEL for females was not identified (≤1 mg/kg/day). Similar lung findings were also observed in the rat carcinogenicity study. In dogs, reversible focal lung discoloration, correlating with alveolar/intra-alveolar foamy macrophages was observed in the 13-week toxicity study. In the 52-week study, minimal to moderate alveolar/intra-alveolar foamy macrophages with or without cholesterol clefts consistent with PLD and accompanied by subacute/chronic inflammation/fibrosis were noted in males at all dose levels and in females at ≥2 mg/kg/day. At the end of 2-month recovery period, findings in the lungs were minimal to slight and were still present in dogs at 4 and 6 mg/kg/day, indicating incomplete, but partial reversibility. The NOEL for PLD was 1 mg/kg/day in female dogs corresponding to 2.3-fold clinical exposure based on cariprazine AUC. A NOEL for males was not identified (≤1 mg/kg/day). PLD-like changes were also observed in mice. In the 6-week study in CByB6F1 hybrid mice, multifocal accumulations of foamy alveolar macrophages were observed in all cariprazine-treated groups with no apparent dose-relation. In the 28-week carcinogenicity study in transgenic Tg.rasH2 mice histiocytic multifocal infiltration was noted at dose levels ≥15 mg/kg/day.

Adrenal gland findings

The adrenal gland was a target organ of toxicity in rats, dogs and mice and included dose-related increases in adrenal gland size/weight, discoloration and cortex hypertrophy/hyperplasia. In a 4-week rat study, multifocal cystic degeneration in zona fasciculate and diffuse dilated sinusoids were observed at a dose level above the MTD. At lower dose levels, vacuolation of the zona fasciculata and diffuse cortical hypertrophy were observed with no NOEL identified. No microscopic changes were seen in the rat 13- and 26-week studies although the adrenal gland was enlarged with increased weight in female rats at ≥12.5 mg/kg/day. In the rat 2-year carcinogenicity study, minimal increases in the incidence of hypertrophy/hyperplasia and vacuolization of the adrenal cortex were observed in male rats at ≥2.5 mg/kg/day.

In the dog 13-week and 52-week studies, enlarged size and increased adrenal gland weight, and foamy vacuolation of the cortical zona fasciculata cells were observed. To further characterise these lesions, electron microscopy was performed on adrenal gland samples in the 13-week study. The EM identified concentric lamellar inclusions within the cytoplasm of adrenal cortical cells or macrophages that were considered morphologically consistent with PLD. In the 52-week study, PLD, as indicated by foamy cytoplasm in the zona fasciculata cells, was observed at all dose levels except at 1 mg/kg/day in male dogs. Similar findings were observed at the end of the 8-week recovery phase indicating a lack of reversibility. Additional, reversible, findings in the cells of the cortical zonae fasciculata and glomerulosa

(arcuata) included hypertrophy/hyperplasia and vesiculation/vacuolation observed at ≥4 mg/kg/day in both sexes. A NOEL for PLD-like changes in the adrenals could not be determined and is ≤1 mg/kg/day and consequently there is no margin of exposure to the clinical exposure. The NOEL for adrenal cortex hypertrophy/hyperplasia and vesiculation/vacuolation is 2 mg/kg/day corresponding to 6.9- and 5-fold clinical exposure based on cariprazine AUC, in male and female dogs, respectively.

In mouse studies, increases in adrenal gland size/weight, discoloration and cortex hypertrophy were noted. In addition, lipofuscin pigment deposition, mainly at the corticomedullary interface, was observed in the 28-week carcinogenicity study in mice.

Ocular findings (cataracts and retinal degeneration)

Effects in the eyes were observed in the 13-week and 1-year toxicity studies in dogs (cataracts, lens degeneration, cystic degeneration and detachment of the retina) and in the 2-year carcinogenicity study in rats (increased incidence and severity of age-related retinal degeneration/atrophy).

In the dog 13-week study, posterior subcapsular cataracts were noted at the ophthalmology examination in 2/5 males and 4/6 females at 8 mg/kg/day. The microscopic investigation revealed minimal to mild lens fiber swelling in the posterior pole of the lens or in the anterior cortex, sometimes in association with the cataracts. During the 4-week recovery period, cataract present at termination of dosing, progressed in 2/4 dogs, and dogs without previous cataracts developed them. The NOEL for the cataracts and the lens fiber swelling was 3 mg/kg/day, corresponding to 8.7- and 7-fold clinical exposure based on cariprazine AUC in male and female dogs, respectively. In a dog ERG study with the same dose levels and duration of treatment, cataracts were also seen in 1/6 males at 3 mg/kg/day and in 5/6 males and 3/6 females at 8 mg/kg/day. In this study, the NOEL for the cataracts in males was 1 mg/kg/day, corresponding to 3.3-fold clinical exposure based on cariprazine AUC, and in females, 3 mg/kg/day, corresponding to 8.8-fold clinical exposure based on cariprazine AUC.

In the dog 52-week study, ophthalmoscopy revealed cataracts in several animals of both sexes at 4 mg/kg/day and in most animals at 6 mg/kg/day, with a dose-related incidence and severity. During the 8-week recovery period, no new cataracts developed but the cataracts seen at the high dose progressed. Like in the 13-week study, lens fiber swelling was observed microscopically, however, at an increased severity and at lower dose levels. Although the severity in males at 1 and 2 mg/kg/day and in females at 2 mg/kg/day was minimal and showed reversibility, the findings progressed in incidence and severity at higher dose levels and are therefore considered as significant. In addition, a non-reversible cystic degeneration of the retina of moderate degree was also observed at ≥4 mg/kg/day. Taken together, the NOEL for the lens fiber swelling in female dogs was 1 mg/kg/day, corresponding to 2.3-fold clinical exposure based on cariprazine AUC while no NOEL was established in male dogs. The NOEL for cataract formation and retinal toxicity was 2 mg/kg/day in both sexes, corresponding to 6.9- and 5-fold clinical exposure based on cariprazine AUC, in male and female dogs, respectively. No cataracts were observed in rats or mice. Retinal degeneration/atrophy was also noted in the 2-year rat carcinogenicity study. This age-related finding occurred in all groups, including controls, but was present with increased incidence and/or severity in cariprazine-treated rats, predominantly in females. To further investigate the potential for retinal toxicity, a 13-week ERG study was conducted in dogs. This study revealed no cariprazine-related retinal effects although cataracts were observed clinically. The NOEL for ERG effects was therefore 8 mg/kg/day, corresponding to 28- and 22-fold clinical exposure based on cariprazine AUC in male and female dogs, respectively.

Effects in female reproductive organs

The female reproductive tract was a target organ in rats and mice, but not in dogs. The changes observed include vaginal epithelial atrophy and mucification in the 28-day study and reduction in the number of corpora lutea in the ovaries, abnormal estrus cycling, and mammary gland hyperplasia and increased secretion in female rats, observed generally in all studies and at all dose levels. Most changes were reversible or partial reversible during the recovery periods. In male rats, there were microscopic alterations in the reproductive tract in the 4-week study at dose levels around or above MTD (12.5 to 50 mg/kg/day), but not in studies of longer duration at lower dose levels or in any other species investigated. In the rat fertility study, cariprazine did not affect male reproduction, whereas female fertility was compromised.

Sciatic nerve findings in rats

Peripheral nerve lesions (myelin fragmentation or axonal degeneration of the sciatic nerve) were noted in the rat 28-day and 26-week studies and in the 2-year carcinogenicity study, but not in dogs or mice. In the 4-week toxicity study, minimal sciatic nerve myelin fragmentation was observed in all rats, including controls although slight increases in severity or incidence was observed at the highest dose levels. The finding was considered as equivocal by the study pathologist. In the 26-week-month toxicity study, axonal degeneration of a minimal degree was observed at a similar incidence in all female rats, including controls. The severity was slightly increased in females at 12.5 mg/kg/day (1 female slight and 1 female moderate). In the 2-year carcinogenicity study, the sciatic nerve fiber degeneration with axonal swelling, digestion chambers containing degraded axonal material, and replacement of axons by connective tissue, was noted in all groups, including controls, but with an increased incidence and/or severity in some cariprazine-treated groups. In males, an increase in the incidence and severity of the sciatic nerve degeneration was observed at the high dose of 2.5 mg/kg/day, 75% in controls, minimal to moderate; versus 92%, minimal to severe. In females, an increased incidence was observed at all dose levels; 55%, 85%, 85%, and 80% animals at 0, 1, 2.5 and 7.5 mg/kg/day, respectively). However, the severity was graded as minimal to severe in most dose groups.

Effects on plasma cholesterol and triglycerides

Plasma cholesterol and triglycerides were significantly decreased in rats, dogs and mice. These decreases were dose-related and reversibility was shown in some studies. In some studies, also body weight gain and food consumption were reduced, but the decreased levels were also observed in some studies in the absence of notable effects on body weight or food consumption.

In rats, marked, but reversible decreases in total cholesterol, HDL and LDL cholesterol, phospholipids, and triglycerides were observed above MTD in the 4-week study. Similar decreases in cholesterol and in triglycerides were seen in the 13- and 26-week studies. In the latter study, decreases were not fully reversible. Decreases were also observed in the 2-year carcinogenicity study. In dogs, dose-related decreases in cholesterol and triglycerides were observed at all dose levels in the 13-week study. Reversibility was observed for cholesterol while triglycerides remained reduced. In this study, a decreased body weight gain was noted at all dose levels in males and at the highest dose (8 mg/kg/day) in females, associated with decreased food consumption at the same dose levels. In the 52-week study, decreased cholesterol was noted in males at all dose levels while only noted in females at the highest dose. Triglycerides were decreased in males at ≥2 mg/kg/day and in females at all dose levels. These alterations were reversible following the 8-week recovery period. In this study, there were no significant effects on body weight gains or food consumption. In mice, dose-related decreases in cholesterol and triglycerides were noted at all dose levels in the 4-week study in CByB6F1 hybrid mice. Reduced body weight gain with no apparent effect on food consumption was also noted at all dose levels.

Genotoxicity

A complete package of genotoxicity studies in agreement with ICH S2(R1) guidance, including test for gene mutations and chromosomal aberrations *in vitro*, and chromosomal aberrations *in vivo*, have been performed with cariprazine. In addition, an *in vitro* mouse lymphoma TK assay was performed. Cariprazine was not mutagenic in the bacterial reverse mutation or in the human lymphocyte chromosomal aberrations assays *in vitro.* In the *in vitro* mouse lymphoma assay, small but statistically significant increases in mutant frequency at cytotoxic concentrations were observed in the absence and presence of metabolic activation. In the *in vivo* micronucleus study, cariprazine was concluded as negative when tested up to the 75 mg/kg/day (MTD). In this study, satellite animals were included and sampled but no TK data were generated. The NOEL of 75 mg/kg corresponds to a HED of 6 mg/kg (corresponding to an approximate daily dose of 300 mg in a 50 kg patient). Based on the negative findings in three mutagenicity studies, the weight of evidence suggests that cariprazine has negligible mutagenic potential.

Carcinogenicity

The carcinogenic potential of cariprazine was evaluated in a 28-week study in Tg-rasH2 transgenic mice and a 2-year carcinogenicity study in Wistar rats. In the 28-week study mouse study, there were no significant increases in neoplastic changes due to cariprazine treatment. All neoplasms are considered incidental and/or due to the common spontaneous tumor incidences in the model. In conclusion, cariprazine up to doses of 15 mg/kg/day in males (18-fold clinical exposure based on AUC) and 50 mg/kg/day in females (53-fold clinical exposure based on AUC) did not induce a significant carcinogenic response in Tg-rasH2 hemizygous mice.

In the 2-year rat study, there were no statistically significant increases in the incidence of tumors in cariprazine-treated males. In females, there was a slight increase in the incidence of benign neoplasms of the adrenal medulla (pheochromocytoma) seen in 4/60 rats, 6.6% at the highest dose 7.5 mg/kg/day. A Pathology Working Group was further involved in the evaluation of this finding and concluded that the increased incidence is likely due to spontaneous variation in the incidence of this common neoplasm in the Wistar rat strain, and not directly related to cariprazine-treatment. In the literature, spontaneous incidences of pheochromocytoma of 1.61% (range 0 to 6%) in aged Wistar rats have been reported (Walsh and Poteracki, 1994). In addition, pheochromocytomas are known to develop in rats following treatment with a wide variety of xenobiotics, and rats appear to be more sensitive than other species (Greaves 2007). In female rats, two other tumors were statistically significant on trend tests (but not pairwise comparisons) and included benign skin fibroma and malignant schwannoma. Based on the low incidences and the lack of statistical significance, the benign skin fibroma and malignant schwannoma are considered incidental and not related to cariprazine treatment. Malignant schwannoma in vagina was observed in 2/60 (3.3%) females at 7.5 mg/kg/day, but none in the other treated or control groups. In literature, a spontaneous incidence of 1.3% (range 0-3.4%) has been reported (Calrus et al 2013). Therefore, the conclusion of the Applicant that there were no cariprazine-related effects on the incidence, distribution or nature of neoplastic changes is agreed with. In conclusion, cariprazine up to doses of 2.5 mg/kg/day in males (5.3-fold clinical cariprazine exposure based on AUC) and 7.5 mg/kg/day in females (13-fold clinical cariprazine exposure based on AUC) did not induce a significant carcinogenic response in Wistar rats.

Reproduction Toxicity

Fertility and early embryonic development

In female rats, longer mean estrous cycle lengths were observed at all dose levels (1 to 10 mg/kg/day), and as a result, extended precoital intervals were noted with lower fertility and conception indices. At 10 mg/kg/day, a decrease in the mean number of implantation sites was noted and as a result, the mean numbers of pups born and live litter sizes were lower than concurrent control values. There was no effect on F_1 postnatal survival and pup body weight through PND 1. Based on above, the NOAEL for female fertility is considered to be lower than 1.0 mg/kg/day and the NOAEL for F1 early embryonic toxicity is 3.0 mg/kg/day. No TK assessments in females were included in this study. The NOAELs correspond to HEDs ≤0.16 and 0.48 mg/kg, respectively.

In male rats, no effects considered cariprazine-related were observed on fertility, copulation or spermatogenic endpoints. The early embryonic developmental toxicity was also unaffected by male cariprazine administration. Based on above, the NOAEL for male fertility and early embryonic developmental toxicity was considered to be 10 mg/kg/day, corresponding to 10-fold clinical exposure based on cariprazine AUC.

Embryo-fetal development

Embryo-foetal development studies were performed with cariprazine in rats and rabbits. In the pivotal rat study, maternal toxicity including clinical signs and reduced body weight gain was observed at ≥2.5 mg/kg/day. The NOAEL for maternal systemic toxicity is 0.5 mg/kg/day, corresponding to 0.7-fold clinical exposure based on cariprazine AUC. Cariprazine caused foetal developmental toxicity at all dose levels (0.5 to 7.5 mg/kg/day) and included reduced foetal body weight, decreased male anogenital distance and skeletal malformations of bent limb bones, scapula and humerus. At dose levels ≥2.5 mg/kg/day, foetal external malformations (localized foetal thoracic edema), visceral variations (undeveloped/underdeveloped renal papillae and/or distended urethrae) and skeletal developmental variations (bent ribs, unossified sternebrae) were observed. The external malformation, localised foetal thoracic edema and additionally a generalized edema, were also seen in the rat DRF study at higher dose levels. Based on above, the NOAEL for embryo-foetal development in rats is lower than 0.5 mg/kg/day corresponding to less than 0.7-fold clinical exposure based on cariprazine AUC.

In the pivotal rabbit study, maternal toxicity was observed as reduced body weight, body weight gains and food consumption at the highest dose evaluated, 5 mg/kg/day. The NOAEL for maternal toxicity is 1 mg/kg/day, corresponding to 1.3-fold clinical exposure based on cariprazine AUC on GD20. There were no significant cariprazine-related effects on pregnancy or foetal parameters at any dose level and the NOEL for embryo-foetal development is 5 mg/kg/day, corresponding to 11-fold clinical exposure based on cariprazine AUC on GD20.

Pre- and post-natal development, including maternal function

In the pivotal study, there was no F_0 maternal systemic toxicity observed at any dose level (0.1 to 1 mg/kg/day). Adverse effects were noted in both the F_1 and F_2 generations of F_0 females given 1 mg/kg/day. In the F_1 generation, cariprazine-related findings include clinical observations (small stature, pale/cyanotic body, gasping, cold to touch), decreased postnatal survival, lower birth weights, body weights and body weight gains during the post-weaning period when compared to controls. In addition, a decreased auditory startle response was observed in males only. In F_1 pups found dead, renal papillae not developed or not fully developed were observed and generally no milk was present in the stomach of pups. The F_1 reproductive performance was unaffected by maternal cariprazine administration. In the F_2 generation, cariprazine-related findings included lower birth weights, clinical signs similar to those in the F_1 generation and lower body weight on post-natal Day 4. Based on above, the NOAEL for maternal systemic toxicity was 1 mg/kg/day, corresponding to 0.9-fold clinical exposure based on cariprazine AUC on GD6. The NOAEL for F_1 and F_2 generation developmental effects was 0.3 mg/kg/day. The maternal cariprazine AUC exposure at this dose level is below the recommended clinical exposure.

Lacteal transfer

A lacteal transfer study in pregnant rats showed that cariprazine and metabolites DCAR and DDCAR are detected in maternal milk at 2 hours post-dose. The milk concentrations of cariprazine were 1.6 to 2.8-fold higher than that in maternal plasma. At 4 hours post-dose, cariprazine was detected in pup plasma at very low levels, while the metabolites DCAR and DDCAR were below the limit of detection (<1 ng/mL).

Local Tolerance

No dedicated local tolerance studies have been conducted with cariprazine. The intended clinical oral administration route was adequately assessed in the repeat-dose toxicity studies.

Other toxicity studies

Metabolites

In humans, two major human metabolites have been identified, DCAR and DDCAR. Both are pharmacologically active metabolites. The genotoxic potential of the metabolite DDCAR was assessed in two *in vitro* studies. DDCAR was not mutagenic in the Ames test. In the chromosome aberration test, a small but statistically significant increased incidence of structural chromosome aberrations was observed in the presence of metabolic activation at the highest concentration evaluated. This concentration was cytotoxic as DDCAR reduced the mitotic index by 54%. No clastogenic signal was noted in the absence of metabolic activation. In the mouse and rat carcinogenicity studies with cariprazine, no significant carcinogenic response was observed. For DDCAR, given the negative Ames test, and the lack of a significant carcinogenicity response with AUC exposure margins of 2.5 to 6 in the mouse carcinogenicity study, but less than 1 in the rat study, the weight of evidence suggests a negligible genotoxic potential for DDCAR.

No dedicated genotoxicity studies were conducted with DCAR. However, DCAR is considered as adequately evaluated in the mouse and rat carcinogenicity studies. The DCAR exposure margins versus clinical AUC exposure are 11- and 30-fold in male and female mice, respectively, and 1.8- and 2.1-fold in male and female rats, respectively. In addition, both DDCAR and DCAR are considered as adequately evaluated in the repeat-dose and reprotoxicology studies.

2.4.5. Ecotoxicity/environmental risk assessment

Cariprazine is a small molecule (Mw <500 g/mol), freely soluble in methanol and poorly soluble in water at pH 7 (1.3mg/L < 100 mg/L; ENV/JM/MONO(2000)6).

While logD exceeds 3, it is unlikely that the substance has potential for bioaccumulation. Considering the data below, cariprazine is not expected to pose a risk to the environment.

Table 1. Summary of main study results

Substance (INN):cariprazine			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.22	Potential PBT N

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.22	not B
	BCF	29-525 L/kg	not B
Persistence	DT50 or ready biodegradability		not P
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined	0.00166 - 0.00697	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.4.6. Discussion on non-clinical aspects

Initially, the Applicant did neither fully evaluate, nor provide an in-depth discussion of the dependence potential of cariprazine, which is mandatory for CNS-active compounds in line with the pertinent European guideline (EMEA/CHMP/SWP/94227/2004). Based on the pharmacological profile e.g. receptor binding (with special regards to preferential affinity for DA D3 receptors) and functional profile (in vitro), DA D3 and D2 receptor occupancy in brain and the in vivo functional data from rat models of cocaine addiction, cariprazine and its major active metabolites (DDCAR, DCAR) are not expected to demonstrate abuse or dependence liability. Furthermore, clinical experiences with antipsychotics displaying receptor profile similar to cariprazine (e.g. aripiprazole or brexpiprazole) have not shown any abuse or dependence liability.

The pharmacokinetics studies appear to have been conducted in accordance with legal requirements and available guidelines. The nonclinical absorption, distribution, metabolism and excretion (ADME) studies have been conducted, IV and PO, in the same species as used in the toxicology studies (PO in rat, dog, rabbit and monkey).

Cariprazine is a lipophilic compound (Mw 427.41), with low pH-dependent solubility (BCS class 2) and high permeability. The single oral dose studies indicate rapid absorption in mouse, rat and dog with Cmax generally observed after 0.5-1 h in rodents, 1-2 h in dogs and after ~ 2 h in monkey. The absolute oral bioavailability was 52-63% in rats and ~ 64-80% dogs, indicating incomplete absorption and some first-pass effect. The apparent elimination half-life ranged from 2 - 3 hrs in rat, 3 – 6 hrs in monkey and 4 - 7 hrs in dog. Co-administration with food had limited effects on cariprazine exposure and PK parameters in animals. No apparent gender differences in PK parameters were noted. There was evidence of limited accumulation of cariprazine, DCAR, and DDCAR (<2-fold) following multiple daily dosing in rodents and dogs, which is, however, in contrast with clinical data.

The in vivo tissue distribution in rat was fast and showed that cariprazine related radioactivity was well distributed into most tissues through 2 hr post-dose, with the tissue/blood ratios >5 in the majority of tissues, indicating accumulation in these tissues. The highest concentrations were found in the organs generally involved in drug absorption (gastrointestinal tract), biotransformation (liver) and excretion (kidney), but high concentration of radioactivity was also found in e.g. adrenal cortex, Harderian gland,

pituitary gland, lungs and in ovary and uterus of female rats. In pigmented rats, there was high amount of radioactivity in skin and choroid layer of the eyes in pigmented rats, suggesting binding to melanin-containing tissues. The elimination was slow from many tissues and radioactivity persisted up to 4 weeks post-dose in adrenal cortex and liver and it was still detected in pigmented skin and in the choroid layer of the eyes at 8 weeks post-dose.

Biotransformation of cariprazine in nonclinical species (rat and dog) and human involves liver P450 metabolism, including demethylation (desmethyl cariprazine and didesmethyl cariprazine), hydroxylation (hydroxy cariprazine) and a combination of demethylation and hydroxylation.

The toxicological profile of cariprazine has been evaluated in a comprehensive set of non-clinical studies in agreement with relevant guidelines.

Ocular toxicity including cataracts and retinal degeneration was observed in several dog studies. In rat distribution studies, the choroid layer of the eye was one of the tissues with the highest [^{14}C] cariprazine-derived radioactivity detected for up to 8 weeks post-dose suggesting melanin-binding and a potential for ocular toxicity. While melanin-binding per se, is not predictive of ocular toxicity, it cannot be excluded that potential release of cariprazine and/or metabolites from melanin may cause high local concentrations of active compound(s). Although the mechanism underlying the cataract development in dogs is unclear, the weight of evidence suggests that the effect may be secondary to the significant decreases in cholesterol and triglycerides in all toxicology species, indicating an effect of cariprazine on lipid synthesis/metabolism. A potential contribution of PLD to the adverse ocular effects seems unlikely as there was no evidence of PLD-related histopathological changes in any of the ocular tissues, including lens and retina.

There is an extensive body of literature indicating that cataracts are induced in animals and/or humans by cholesterol lowering drugs acting at different steps in the cholesterol biosynthetic pathway; HMG-CoA reductase (lovastatin), oxidosqualene cyclase (OSC) (U18666A) or 3-beta-hydroxysterol delta-24-reductase (triparanol). In dogs, cataracts have been found in safety studies of lovastatin, fluvastatin, and simvastatin. Also in humans, statin therapy seems to be associated with an increased risk of cataract development. Another marketed product that causes cataracts in dogs is Seroquel (quetiapine fumarate), a psychotropic agent found to cause posterior, axial triangular cataracts in dogs. The exact mechanism by which Seroquel causes cataracts in dogs is unknown, but dose-dependent reduction in plasma cholesterol was observed and interference with cholesterol biosynthesis was suspected. To date, there appears not to be an association of Seroquel treatment and cataract formation in humans. A correlation between cataract development and cholesterol metabolism is also seen in some inherited diseases in man. The Smith-Lemli-Opitz syndrome, mevalonic aciduria and cerebrotendinous xanthomatosis all involve mutations in enzymes of cholesterol metabolism, and are associated with increased risk of cataracts. The cause of cataracts in these diseases was postulated to be due to the decrease in cholesterol level in the lens. Support for this hypothesis was derived from a hereditary cataractous rat strain, Shumiya cataract rat, where mutations were identified in genes which function in the cholesterol biosynthesis pathway. Cataract onset was associated with a specific combination of mutant alleles that decreased cholesterol levels in cataractous lenses to about 57% of normal.

In summary, the mechanism of the cataract formation in dogs has not been fully established. Based on available literature, it is agreed that there is an association between reduced cholesterol levels and cataract formation and that dogs seem a sensitive species, and that this may be a plausible explanation. However, as there were no significant reductions noted in blood cholesterol in human clinical trials and that an association of cariprazine-treatment and lenticular changes and potentially also cataracts cannot currently be fully excluded, other potential/additional mechanisms may be involved. Cataracts were proposed to be included as a potential important risk in the RMP and warnings included in section 4.8 of the SmPC.

Apart from cataracts, retinal detachment/cystic degeneration were observed at doses ≥4 mg/kg/day in the 52-week dog study. As further clarified by the Applicant, the retinal changes were limited to animals with hypermature cataracts and associated lens resorption. As there was a 100% correlation between the retinal changes and advanced stage of cataract, the dog retinal changes are considered likely secondary to the cataracts and not due to a direct retinal toxicity. Additionally, literature describes uveitis-induced retinal lesions similar to those observed in the 52-week dog study and mild uveitis was present in eyes with resorbing cataracts. Regarding the retinal changes observed in the 2-year rat study, it is agreed with the Applicant that the etiology of the retinal findings are different in rats and dogs and that the findings in rats likely represent an exacerbation of common background lesions associated with behavioral changes and/or increased survival affecting exposure to light and are found with drugs acting on the CNS. This albino rat-specific response is not considered to represent a risk to humans. Taken together, the available data do not indicate a direct retinal toxicity of cariprazine. Available clinical data do not indicate retinal toxicity.

The adrenal gland was a target organ of toxicity in rats, dogs and mice. The Applicant suggests several plausible mechanisms for the observed adrenal effects, including ACTH stimulation caused by stress, 5HT1A agonism, or hyperprolactinemia, and secondary effects due to the decreased cholesterol levels. Based on the available data, all proposed mechanisms seem reasonable, and do not indicate a direct toxicity of carprazine of the adrenal gland.

The adrenal gland changes seen in the early rat studies at high dose levels around the MTD are considered likely stress-related. In the longer studies (≥13 weeks), a potential role of 5HT1A agonism was also proposed. In the literature, 5HT1A agonists have been reported to induce increase in serum ACTH (and prolactin) levels in rats. In toxicity studies with aripiprazole, another antipsychotic drug similar 5HT1A partial agonist properties as cariprazine, adrenal cortex hypertrophy with normal adrenocortical function as evidenced by significantly increased circulating levels of ACTH and corticosterone has been reported in rat studies. In addition, hyperprolactinemia has been shown to induce secretion of ACTH, and hyperprolactinemic rats and mice have been reported to show an increased adrenal weight without any associated histological changes. As the effects were most prominent in female rats and data showing that cariprazine induced hyperprolactinaemia to a greater extent in female rats, disturbed regulation of prolactin appears to be a possible mechanism. Finally, plasma cholesterol reduction was consistently observed being greatest in high dose females in all rat studies (81%, 64% and 60% in the 13-, 26- and 104-week studies, respectively). Literature data support that drugs with inhibitory effects on cholesterol synthesis can produce adrenal cortical hypertrophy/hyperplasia.

In mice, the adrenal effects are likely related to cariprazine´s pharmacological properties. Hyperprolactinemia-related reproductive tract changes were observed at all dose levels in all studies. As further discussed by the Applicant, increased potassium levels were observed at all dose levels in both sexes in the 6- and 7-week studies with a potential relationship to the adrenal lesions. In the literature, hyperkalaemia is a proposed as a possible diagnostic feature of compromised functionality of the adrenal cortex. Although no overt adrenal gland toxicity was observed and this change occurred without other possible associated signs of adrenal insufficiency such as hyponatremia, hypochloremia and hypoglycemia, consistent occurrence at all dose levels in two studies suggests that it cannot be dismissed and it seems to be reasonable to consider it as a likely consequence of a slight deficiency in adrenocortical function. A potential impairment of adrenal function may be related to the decreased cholesterol levels since the biosynthesis of steroid hormones in the adrenal cortex is initiated by the utilization of available free plasma cholesterol or stored pools of labile cholesterol. Group mean reductions in plasma cholesterol levels ranged from 51 to 88% in males and from 54 to 73% in females. Accordingly, in mice a slight insufficiency of adrenocortical function cannot be ruled out and the decreased cholesterol levels is considered as a likely mechanism while in the induction of adrenocortical hypertrophy, 5HT1A agonism and hyperprolactinaemia could also have contributory roles.

In dogs, the adrenal gland findings are considered likely related to chronic stress, as dose-related slight to marked thymic lymphoid cell depletion/atrophy, which is a common age- and stress-related finding, was present in all animals, but was most severe at ≥4 mg/kg/day. A relation of the observed PLD and the adrenal gland findings is considered unlikely as the PLD persisted during the 8 weeks recovery period of the 52-week study while the adrenal gland findings were reversible.

Taken together, the mechanism for the adrenocortical changes is likely multifactorial with the most likely contributors being generalized stress (rats, dogs), pharmacological action via 5HT1A agonism (rodents) and/or an effect on prolactin regulation (rodents), and an effect on lipid metabolism (all species). The preclinical adrenal gland findings are not indicative of overt adrenocortical toxicity or adverse functional changes with the exception of mice where a slight functional deficit cannot be ruled out potentially caused by prominent reduction of plasma cholesterol, an important source of the biosynthesis of steroid hormones. The relevance and significance of the adrenal changes and proposed mechanisms to humans is likely to be limited as there was no clear signal for either adrenal toxicity, hyperprolactinaemia or significantly reduced plasma cholesterol in the human clinical trials. Taken together, the adrenal gland changes observed in non-clinical studies are likely of low relevance for the human situation.

Cariprazine caused phospholipidosis (PLD) sometimes associated with subacute/chronic inflammation, and haemorrhage in the lungs of rat, dog and mouse. PLD is commonly associated with cationic amphiphilic agents such as cariprazine. As further outlined by the Applicant, PLD-associated inflammatory changes as consequences of prolonged PLD are often seen in chronic toxicity studies and the changes seen in the cariprazine toxicology studies do not differ from that described in the literature. The functional consequences of the observed lung PLD remain uncertain, although there were no obvious functional deficits in the affected animals. Taken together, it is agreed that the observed lung findings in cariprazine toxicology studies are similar to that commonly observed in toxicity studies after administration of CADs and are unlikely to represent a significant human risk. Although the human relevance is unclear, there were no relevant AEs observed in the clinical database with regard to respiratory/pulmonary symptoms. In addition, the findings are expected to be reversible following drug discontinuation. Therefore, it was agreed that no further risk minimisation measures are deemed necessary.

Plasma cholesterol and triglycerides were significantly decreased in rats, dogs and mice. These decreases were dose-related and reversibility was shown in some studies. In some studies, also body weight gain and food consumption were reduced, but the decreased levels were also observed in some studies in the absence of notable effects on body weight or food consumption. The underlying mechanism of the decreased cholesterol and triglyceride levels are not clear. While general malnutrition may have contributed to the decreases in cholesterol and triglyceride levels in some rat and mouse studies, the most likely potential mechanism is that cariprazine inhibits the synthesis of cholesterol and triglycerides. In the clinical trials there was no significant reduction in blood plasma cholesterol and triglycerides therefore clinical consequences are considered unlikely.

The observed effects in female reproductive organs are likely caused by cariprazine´s D2 receptor blocking activity resulting in prolactin elevations. Evaluation of prolactin levels was not included in repeat-dose toxicity studies, but in an investigative 14-day study in female rats, cariprazine increased mean prolactin levels 87- and 256-fold control values at 0.1 and 1 mg/kg/day, respectively. Prolactin-mediated effects are also evident in the rat fertility study. However, in cariprazine clinical trials, there were no noteworthy effects on prolactin levels.

The peripheral nerve lesions seen in rats are considered as equivocal. An additional review of the lesions seen in the 26-weeks toxicity and 2-year carcinogenicity studies in rats was conducted by a veterinary neuropathologist with the conclusion that cariprazine may exacerbate the age-related spontaneous neuropathic process and given the frequency of the spontaneous sciatic nerve neuropathy findings, the toxicological significance of these findings relative to test article administration appears questionable. The

reviewer also noted that the overall incidence of the sciatic nerve lesions in rats was very low, and that no peripheral nerve lesions were observed in dogs and mice. Therefore, the relevance of this finding to human risk is unknown but appears to be unlikely.

In the rabbit embryo-foetal development study, no adverse effects where noted at cariprazine AUC exposures corresponding to 11-fold clinical exposure. In rats, external and skeletal malformations were observed with a NOAEL at exposures below the recommended clinical exposure. Placental transfer of cariprazine and metabolites DDCAR and DCAR was confirmed in both rats and rabbits. In rats, the pup cariprazine exposure was approximately similar to maternal levels, while in rabbits the pup cariprazine exposure was approximately 20% of maternal levels. In the pre- and postnatal development study, adverse effects were noted in the F_1 generation in the absence of significant maternal toxicity. Effects were also noted in the F_2 generation which is highly unusual. The maternal/offspring exposure assessment in various studies indicate that the rat foetal *in utero* cariprazine exposure is similar to the maternal exposure, while post-natal cariprazine exposure is negligible. The adverse findings in rats (both teratogenic effects in the developmental toxicity study, as well as adverse effects in the F_1-generation and unusual adverse findings in F_2-generation observed in the peri- and postnatal study) raises serious concerns regarding exposure in pregnancy as well as of women of child bearing potential. For the intended target population this potential important risk maybe particularly challenging to handle at clinical use. It was therefore recommended that reproductive toxicity is included as an important potential risk in the RMP and that adequate warnings are included in the SmPC.

The two major human metabolites, DCAR and DDCAR are considered as adequately evaluated in genotoxicity/carcinogenicity, repeat-dose and reprotoxicology studies. According to the Applicant, a mass balance study of cariprazine in humans following oral administration of [^{14}C] cariprazine was not feasible as cariprazine and/or its metabolite(s) have strong affinity to the eyes of pigmented rats. Consequently, there is insufficient understanding of the circulating drug-related material in plasma and it is therefore not possible to conclude that all human metabolites have been adequately evaluated in non-clinical species. Based on additional data provided by the applicant, and given the potential risk for lenticular changes and cataracts, the CHMP established that a radioactive mass balance study in humans is not necessary. The available data indicate a low risk for the occurrence of a unique major human metabolite. If present, a potential risk for a mutagenic or carcinogenic potential may be regarded as low as the cariprazine metabolites share the predominant structural moieties of the parent substance, and as neither cariprazine, nor its major human metabolites DCAR and DDCAR unveiled any mutagenic or carcinogenic potential.

2.4.7. Conclusion on the non-clinical aspects

The non-clinical data provided were considered sufficient together with additional measures as specified in the discussion section to support this dossier.

2.5. Clinical aspects

2.5.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Study title	Study design	N:o of patients	Duration
RGH-PK-10 (2007) USA	Single-Center, Randomized, Open-label, Parallel-Group, Single-Dose Study Assessing the Effects of Food and Gender on the Pharmacokinetics of RGH-188 2-mg Tablet in Healthy Volunteers (Phase 1: Bioavailability study)	Single dose, gender and food effect study	42	Single dose
RGH-PK-14 (2012) USA	Single-Center, Randomized, Open-Label, Parallel-Group, Single-Dose Study Assessing the Effect of Food on the Pharmacokinetics of Cariprazine 1.5-mg To-Be-Marketed Capsule in Healthy Volunteers (Phase 1: Bioavailability study)	Single-center, randomized, open-label, parallel group, single-dose, food effect study	50	Single dose
RGH-188-001 (2005-2007) UK	A Study to Examine the Safety,Tolerability, and Pharmacokinetics of Escalating Single Oral Doses of RGH-188 in Healthy Male Volunteers (Phase 1 study)	Part 1: Randomized, double-blind, placebo-controlled, rising single-dose PK, tolerability Part 2: Randomized, open-label, single-dose, crossover food effect study	40	Single dose
A002-A1 (2006-2007) Japan	Clinical Pharmacology Study of MP-214 in Healthy Adult Males	Randomized, double-blind, placebo controlled, single-dose, PK study	24	Single dose
A002-A2 (2006-2007) Japan	Clinical Pharmacology Study of MP-214 in Healthy Adult Males (Phase 1: Repeated Administration, PK study)	Randomized, double-blind, placebo controlled, multiple-dose, PK study	20	14 days
RGH-188-002 (2005-2007) UK	A Study to Examine the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of Multiple Oral Doses of RGH-188 in Healthy Male Volunteers (Phase 1: PK study)	Randomized, double-blind, placebo controlled, multiple-dose, PK study	32	Cohort 1: 13 days Cohort 2: 14 days Cohort 3: 14 days Cohort 4: 21 days
RGH-188-101 (ongoing) UK	A Single-Dose Study to Evaluate the Pharmacokinetic, Safety, Tolerability Profile and the Effects of Food on the Pharmacokinetics of Different Formulations of Cariprazine in Healthy Male Subjects (Phase 1: PK study)	Single-center, randomised, open- label, parallel-group, single dose study in healthy Caucasian male volunteers Part 1: Open-label, randomised, parallel-group trial, evaluating the pharmacokinetics, safety and tolerability of two prolonged release and one immediate release formulation Part 2: Open-label, single- or two- arm, single-dose trial assessing the effect of food on the pharmacokinetics of the prolonged release formulation(s) of	Part 1: 120 Part 2: 20/arm	Single dose

Study	Study title	Study design	N:o of patients	Duration
		cariprazine selected in Part 1.		
RGH-MD-01 (2006-2008) USA	A Double-blind, Randomized, Placebo-Controlled Trial of the Safety, Tolerability and Pharmacokinetics Following Escalating, Multiple, Oral Doses of RGH-188 in Patients With Schizophrenia (Phase 1b: PK study)	Randomized, double-blind, placebo controlled, multiple cohort, group sequential, dose escalating study	62	up to 41 days
RGH-MD-18 (2010-2012) USA	A Randomized, Double-blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Cariprazine Following Escalating Multiple Oral Doses in Patients with Schizophrenia (Phase 1b: PK study)	Randomized, double-blind, placebo controlled, multiple cohort, group sequential, dose escalating, PK study	36	28 days
RGH-PK-04 (2011-2012) USA	A Pharmacokinetic Study of Cariprazine (RGH-188) in Healthy Subjects and Patients With Impaired Hepatic Function (Phase 1: PK study)	Phase 1, open-label, parallel group, single and multiple dose, hepatic impairment study	Part A: 24 Part B: 24 (13 of them enrolled in Part A)	Part A: single dose Part B: 14 days
A002-A6 (2011) Japan	Clinical Pharmacology Study of MP-214 with Healthy Adult Japanese, South Korean, Taiwanese, and Caucasian Males as Subjects (Phase 2 study)	Open label, single-dose, parallel group, comparative study	50	Single dose
RGH-PK-07 (2007-2010) USA	A Single-Center, Randomized, Open-Label, Parallel-Group, Multiple-Dose Study of the Drug-Drug Interaction Between RGH-188 and Ketoconazole in Healthy Subjects (Phase 1: PK study)	Randomized, open-label, parallel group, multiple dose, drug-drug interaction study	36	Group A: 20 days Group B: 14 days
RGH-188-003 (2005-2007) UK	A Study to Examine Striatal Dopamine D2-Receptor Occupancy After Single and Multiple Oral Doses of RGH-188 in Healthy Male Volunteers Using Positron Emission Tomography With the D2-Receptor Ligand [11C]-Raclopride (Phase 1: PD and PK/PD study)	Open-label, single- and multiple dose receptor occupancy	Cohort 1: 2 subjects Cohort 2: 3 subjects	Cohort 1: single dose Cohort 2: 14 days
RGH-MD-02 (2012) USA	Evaluation of the Effects of Sequential Multiple-dose Regimens of Cariprazine on Cardiac Repolarization in Patients With Schizophrenia (Phase 1b: PD and PK/PD study)	Randomized, double-blind, placebo- and moxifloxacin controlled, parallel group, multiple dose, intensive QT study	129	35 days DB + 7 days follow- up

Study	Study title	Study design	N:o of patients	Duration
RGH-MD-14 (2007) USA	A Clinical Trial to Determine Striatal and Extrastriatal Dopamine D3/D2 Receptor Occupancy after Multiple Oral Doses of RGH-188 in Schizophrenic Patients Using Positron Emission Tomography With the D3/D2-Receptor Ligand [^{18}F] Fallypride (Phase 2b: PK/PD study)	Open-label, multiple dose, receptor occupancy	8	14 days
RGH-PK-15 (2012-2015) USA	A Study to Characterize the Dopamine D3 and D2 Receptor Occupancy in Various Regions of the Brain After Multiple Oral Doses of Cariprazine in Patients With Schizophrenia Using Positron Emission Tomography With the D3/D2 Receptor Ligand [11C]- (+)-PHNO (Phase 1: PK/PD study)	Open-label, multiple-dose, receptor occupancy, 3-cohort study in patients with schizophrenia	9	25 days
RGH-MD-03 (2007-2008) USA	A Double-blind Placebo-Controlled Evaluation of the Safety and Efficacy of RGH-188 in the Acute Exacerbation of Schizophrenia (Phase 2: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, flexible-dose, efficacy and safety study	392	6 weeks DB + 4 weeks follow-up
RGH-MD-04 (2011-2012) USA, Romania, Russia, Ukraine	A Double-blind, Placebo and Active- Controlled Evaluation of the Safety and Efficacy of Cariprazine in the Acute Exacerbation of Schizophrenia (Phase 3: Efficacy and safety study)	Randomized, double-blind, placebo-and active controlled, parallel group, fixed-dose, efficacy and safety study	617	6 weeks DB + 2 weeks follow-up
RGH-MD-05 (2011-2012) USA, Colombia India, South Africa	A Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in the Acute Exacerbation of Schizophrenia (Phase 3: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, fixed/flexible dose, efficacy and safety study	446	6 weeks DB + 2 weeks follow-up
RGH-MD-16 (2009-2010) USA, India, Russia, Ukraine, Malaysia	Evaluation of the Safety and Efficacy of RGH-188 in the Acute Exacerbation of Schizophrenia (Phase 2b: Efficacy and safety study)	Randomized, double-blind, placebo- and active controlled, parallel group, fixed-dose, efficacy and safety study	732	6 weeks DB + 2 weeks follow-up
RGH-MD-06 (2014-2015) USA, India, Romania, Slovakia, Ukraine	A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Cariprazine (RGH-188) in the Prevention of Relapse in Patients with Schizophrenia (Phase 3: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, flexible- and fixed-dose efficacy and safety study	765	20 weeks of open-label, 26-72 weeks of double blind, 4 weeks follow-up

Study	Study title	Study design	N:o of patients	Duration
RGH-188-005 (2014-2015) Croatia, Czech Republic, France, Hungary, Russia, Ukraine, Poland, Romania, Serbia, Spain, Bulgaria	A Randomized, Double-blind, Parallel-group Study to Investigate the Efficacy, Safety, and Tolerability of Cariprazine in Patients with Predominant Negative Symptoms of Schizophrenia Active control: risperidone (Phase 3b: Efficacy and safety study)	Randomized, Double-blind, Parallel-group Efficacy, Safety, and Tolerability Study	461	The 26-week double-blind treatment period comprised 2 phases: a 14-day study treatment up- titration phase followed by a 24-week study treatment continuation phase
A002-A3 (2009) Japan	Study of MP-214 in Patients With Schizophrenia (Exploratory Study) (Phase 2 : Efficacy and safety study)	Randomized, open-label, fixed-dose, parallel group, PK and exploratory efficacy and safety study	35	14-day fixed-dose treatment period
A002-A4 (Ongoing) Japan, Korea, Taiwan	Study of MP-214 in patients with schizophrenia (Confirmatory study) (Phase 2/3: Efficacy and safety study)	Randomized, double-blind, placebo- and risperidone-controlled, parallel-group, fixed- dose study	508	6 weeks
A002-A5 (Ongoing) Japan, Korea, Taiwan	The long-term safety, tolerability, and efficacy of MP-214 in patients with schizophrenia (Long-term extension study) (Phase 2/3: Efficacy and safety study)	1) Double-Blind Treatment Period (until the End of Week 6 of the Treatment Period) Multinational, multicenter, randomized, double-blind, risperidone-controlled, parallel- group, fixed-dose study 2) Open-Label Treatment Period (after Week 6 of the Treatment Period) Multinational, multicenter, randomized, open-label, flexible- dose study	254	6 weeks double-blind and 42 weeks open-label treatment
A002-A8 (2014-2015) Japan	A Long-Term Study of MP-214 in Patients With Receiving Multiple Drugs (Phase 3: Safety study)	Joint multicenter, unblinded, variable-dose study	42	48 weeks
A002-A9 (2014-2015) Japan	A Clinical Pharmacology Study (Drug Elimination Study) of MP-214 in Healthy Adult Male Subjects (Phase 2/3: PK study)	Unblinded, randomized (after final dose of investigational product), control not treated with medicinal carbon (carbon treatment period), parallel group comparison (carbon treatment period)	8	14 days
A002-A10 (2013) Japan	A Study to Evaluate the Bioequivalence of MP-214 between Tablet and Capsule in Healthy Subjects	Open-label, single-dose, randomized, 2-period × 2-treatment crossover study	44	Single-dose

Study	Study title	Study design	N:o of patients	Duration
	(Phase 2/3: Bioequivalence study)			
A002-A11 (2013-2014) Japan	Clinical Pharmacology Study of MP-214 in Patients with Schizophrenia (12-week Treatment) (Phase 2/3: PK study)	Multicenter, randomized, open- label, fixed-dose study Parallel-group comparison	38	12 weeks + 12 weeks follow- up
RGH-MD-11 (2013) USA, Colombia, India, Romania, Russia, Ukraine	Evaluation of the Long-Term Safety, Tolerability, and Pharmacokinetics of Cariprazine in Patients With Schizophrenia (Phase 3: Safety study)	Long-term, open-label, flexible- dose, safety study enrolling completers from lead-in studies RGH-MD-04 and RGH-MD-05 and new patients	586	48 weeks open-label treatment
RGH-MD-17 (2010-2012) USA, India, Russia, Ukraine, Malaysia	A Long-term, Open-label Extension Study of the Safety and Tolerability of RGH-188 (Cariprazine) in Patients With Schizophrenia (Phase 2b: Safety study)	Long-term, open-label, flexible-dose, outpatient, extension of RGH-MD-16	93	53 weeks up to 1 week screening, 48 weeks open- label treatment, 4 weeks safety follow up
RGH-MD-31 (2008-2009) USA, India, Russia	A Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of RGH-188 in Patients With Acute Mania Associated With Bipolar I Disorder (Phase 2: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, flexible-dose efficacy and safety study	238	3 weeks double-blind treatment + 2 weeks follow- up
RGH-MD-32 (2011-2012) USA, India	A Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Acute Mania Associated With Bipolar I Disorder (Phase 3: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, flexible-dose efficacy and safety study	312	3 weeks double-blind treatment + 2 weeks follow- up
RGH-MD-33 (2011-2012) USA, Ukraine, Romania, Russia, Serbia, Croatia	A Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Acute Mania Associated With Bipolar I Disorder (Phase 3: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, fixed/ flexible-dose efficacy and safety study	497	3 weeks double-blind treatment + 2 weeks follow- up
RGH-MD-36 (2012) USA, Germany, Hungary, Poland, Spain	A Long-term Open-label Study of the Safety and Tolerability of Cariprazine in Patients With Bipolar I Disorder (Phase 3: Safety study)	Long-term, open-label, flexible-dose, safety study	402	16 weeks open-label treatment
RGH-MD-52 (2010-2011) USA	A Double-blind, Placebo-Controlled Study of RGH-188 (Cariprazine) in Bipolar Depression (Phase 2: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, efficacy and safety	233	8 weeks double-blind treatment + 2 weeks follow- up

Study	Study title	Study design	N:o of patients	Duration
RGH-MD-56 (2014) USA, Canada, Bulgaria, Russia, Ukraine, Colombia	A Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar Depression (Phase 2b: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, fixed-dose efficacy and safety study	584	8 weeks
RGH-MD-71 (2010-2012) USA	A Double-blind, Placebo-Controlled Study of Cariprazine (RGH-188) as Adjunctive Therapy in MDD (Phase 2: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, flexible-dose efficacy and safety	231	8 weeks
RGH-MD-72 (Ongoing) USA	Double-Blind, Placebo-Controlled Study of Cariprazine as Adjunctive Therapy in Major Depressive Disorder (MDD) Placebo + ADT (Phase 3: Efficacy and safety study)	8-week of open label ADT + single blind placebo, followed by 8 week double blind treatment period on cariprazine + ADT or placebo + ADT for inadequate responders and ADT + single blind placebo for responders, followed by a 1-week safety follow-up period	500	16 weeks
RGH-MD-75 (2013-2014) USA, Finland, Estonia, Ukraine, Slovakia, Sweden	A Double-blind, Placebo-Controlled Study of Cariprazine (RGH-188) as Adjunctive Therapy in Major Depressive Disorder (Phase 2b: Efficacy and safety study)	Randomized, double-blind, placebo controlled, parallel group, flexible-dose efficacy and safety study	819	8 weeks
RGH-MD-76 (Ongoing) USA	A Phase 3, Long-Term, Open-Label Study of Safety and Tolerability of Cariprazine as Adjunctive Therapy in Major Depressive Disorder (Phase 3 safety and tolerability study)	Multicenter, open-label, long- term, flexible-dose study in adult patients with a primary diagnosis of major depressive disorder	500	26 weeks OL + 2 weeks follow-up
A002-A7 (2015) Japan	A Long-Term Study Of MP-214 In Patients With Chronic Phase Or Elderly Schizophrenia (Phase 3 safety)	Phase 3 randomized, unblinded risperidone-controlled, parallel- group fix-flexible dose study	125	48 weeks OL + 12 weeks follow-up

2.5.2. Pharmacokinetics

Absorption

Cariprazine has pH dependent solubility. At pH 6, 5 mg could be dissolved in 250 mL minimizing the need for a study with a PPI. No absolute bioavailability study was performed.

Administration of a high-fat breakfast delayed the absorption of cariprazine (median Tmax increased from 4 hours to 9 hours), increased the AUC0-∞ by ~12%, decreased the Cmax by < 5%, and did not change

the terminal elimination half-life. The effect of food on the exposure of DCAR and DDCAR metabolites was also minimal.

The intended to be marketed capsule was used in the phase 3 studies.

Distribution

Cariprazine is highly bound to plasma proteins with an unbound fraction of 0.04. The metabolites DCAR and DDACR have unbound fractions of 0.05 and 0.07, respectively. All three active moieties protein binding was independent of concentration except a slight concentration dependency for DCAR and DDCAR. However the effect was minimal in the concentration range used.

The concentrations of cariprazine, DCAR, and DDCAR in cerebrospinal fluid were approximately 5%-10%, 4%-6%, and 3%-8% of the respective concentrations in plasma following subchronic administration for 15 days. Plasma:blood ratio of cariprazine was approximately 1.2-1.3.

The apparent volume of distribution (Vz/F) determined in multiple dose studies by non-compartmental analysis is about 1000 L.

Elimination

The half-life of cariprazine is between 1 and 3 days. The metabolites DCAR has a half-life of 1 to 2 days and DDCAR half-life is ranging between 2 to 3 weeks, but the determination is uncertain.

Based on population PK analysis, the effective half-life leading to steady state is about 1 to 1.5 day for cariprazine and DCAR and 6 to 9 days for DDCAR. Approximately 90% of steady state is reached in about 4 to 5 days for cariprazine and DCAR and 21 to 31 days for DDCAR.

Average values of cariprazine oral clearance (CL/F) were usually between approximately 20 L/h and 30 L/h.

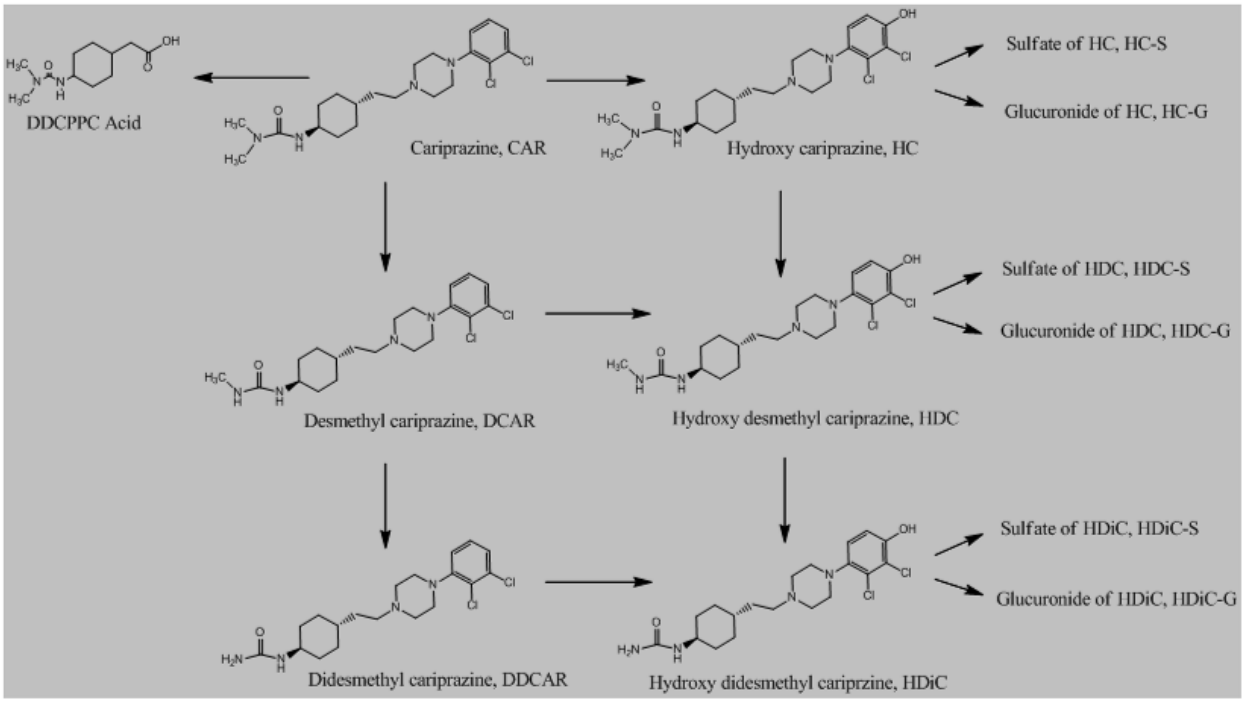
Excretion

No mass-balance study following oral administration of [^{14}C] cariprazine was performed. The excretion and metabolism of cariprazine in humans was studied following oral administration of multiple doses of cariprazine hydrochloride to three schizophrenic patients by collecting plasma and excreta on day 26 and 30. The daily dose was 12.5 mg.

The overall average daily excretion of cariprazine and its metabolites in urine for the 3 patients was 21% of the daily dose. Approximately 1.2% of the daily dose was excreted in urine as unchanged cariprazine. The major metabolite excreted in urine was DDCPPC acid and it accounted for approximately 6.6% of the daily dose. Approximately 4.0 and 0.4% of the daily dose were excreted as the DDCAR and DCAR metabolites in urine, respectively.

The overall average daily excretion of cariprazine and its metabolites in faeces for the three patients was approximately 40 % of the daily dose. Approximately 3.7% of the daily dose was excreted as unchanged cariprazine. The major metabolite excreted was hydroxy-cariprazine (HC) and it accounted for approximately 23% of the daily dose. Similar amount of hydroxy-DCAR (4.3% of the daily dose), hydroxy-DDCAR (5.1% of the daily dose) and DDCAR (3.5% of the daily dose) metabolites was excreted in faeces. Only a trace amount of the dose was excreted in faeces as the DCAR metabolite (0.7% of the daily dose).

Figure 1 Proposed metabolic pathway of cariprazine

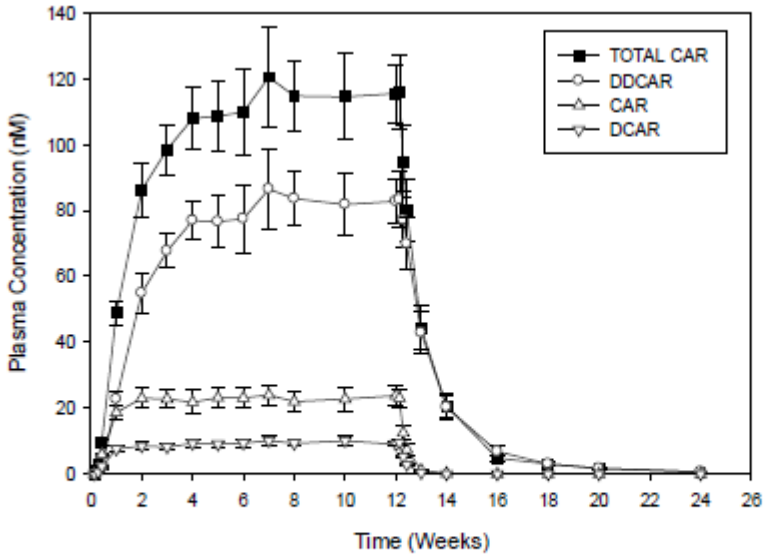


Total excretion in the three patients was 42, 67% and 73%, of the administered dose respectively.

Metabolism

In vitro incubations show that both CYP3A and CYP2D6 are involved in the metabolism of cariprazine. Based on the *in vitro* data the formation of DCAR both CYP3A4 and CYP2D6 seems to be involved. The in vitro formation of DDCAR from DCAR was minimally inhibited by ketoconazole and quinidine indicating minor involvement of CYP3A and CYP2D6. DDCAR elimination seems to involve minor CYP3A4 as only trace amounts of hydroxy-DDCAR could be found after incubations with recombinant CYP3A4. Other enzymes might therefore be involved in the elimination of DDCAR.

In clinical studies a number of plasma metabolites were found circulating and in most studies the two active metabolites DCAR and DDCAR have been evaluated. After multiple administrations the exposure to DCAR was 30-35% of the AUC of cariprazine. The exposure to DDCAR was a least 2-fold higher than that of cariprazine.



Source: Study A002-A11, Tables 14.2-1, 14.2-2, 14.2-3, and 14-2-16 for CAR, DCAR, DDCAR, and Total cariprazine, respectively. Values for CAR, DCAR, and DDCAR were converted to nM for plotting purposes based on MW of 427, 413, and 399, respectively.

Consequences of possible genetic polymorphism

The enzyme CYP2D6 may be involved in the metabolism of cariprazine based on *in vitro* metabolism data. There was no dedicated CYP2D6 genotype pharmacokinetic study. The effect of CYP2D6 genetic polymorphism was however evaluated in the population pharmacokinetic analysis.

There were 868 patients classified as extensive metabolizers (EMs; defined as ultra, extensive, and intermediate metabolizers) and 40 patients classified as poor metabolizers (PMs). The effect of CYP2D6 metabolizer status was evaluated by comparing the distribution of empirical Bayesian estimates (EBE's) between different categories of CYP2D6 metabolizer status There were no statistically significant differences (α = 0.05) for cariprazine, DCAR, DDCAR, or Total Cariprazine moiety exposures for PM patients as compared to EM patients.

Special Populations

No study was performed in subjects with renal impairment. The population PK analysis included data from 2844 patients. Among these patients, 520 (18%) had mild renal impairment, 24 (1%) had moderate renal impairment, and 2300 (81%) had normal renal function. There was no statistically significant relationship identified between plasma clearance of either moiety and creatinine clearance. The use of cariprazine in severe renal impairment has not been investigated.

A study was performed in mild and moderate hepatic impairment using both single (1 mg) and multiple dosing for 14 days using 0.5 mg. The results showed that compared to healthy subjects, subjects with either mild or moderate hepatic impairment had up to ~25% higher exposure for cariprazine and up to ~45% lower exposure for DCAR and DDCAR (see below). The unbound fraction was not determined in this study. However *ex vivo* plasma samples were used to investigate whether unbound data would change the conclusions. The SmPC recommendations did not change when unbound data was included.

Compound		Mild/Healthy	Moderate/Healthy
Part A day 1	**AUC change**	+20%	-13%

(1.0 mg)	Cariprazine	**Cmax change**	+3%	-5%
	Desmethyl cariprazine	**AUC change**	-30%	-33%
		Cmax change	-36%	-29%
	Didesmethyl cariprazine	**AUC change**	-31%	-45%
		Cmax change	-24%	-32%
Part B day 14 (0.5 mg)	Cariprazine	**AUC change**	+3%	+26%
		Cmax change	+4%	+23%
	Desmethyl cariprazine	**AUC change**	-15%	-21%
		Cmax change	-19%	-27%
	Didesmethyl cariprazine	**AUC change**	-34%	-32%
		Cmax change	-34%	-28%

Pharmacokinetics of cariprazine has not been evaluated in paediatric subjects (<18 years of age) and in the elderly (>65 years of age).

Race, gender and body weight were found to be covariates in the final population PK analysis, however the covariate effects are generally small and no dose adjustment is proposed.

Pharmacokinetic interaction studies

Effects of cariprazine on the pharmacokinetics of other drugs

Table 1. Cut offs used in the evaluation of DDI potential for cariprazine, DCAR and DDCAR

Dose		**C_{max}** [a]	**C_{max}**	**$C_{max,u}$**	**$C_{max,u}$*50**	**25*Inlet$C_{max,u}$**	**0.1* dose /250mL**
(mg)		(ng/mL)	(µM)	(µM)	(µM)	(µM)	(µM)
6	Cariprazine[a]	22.7	0.83	0.0021	0.11	1.11	5.62
	DCAR	5.96	0.014	0.0007	0.036	1.38	-
	DDCAR	35.9	0.1	0.0072	0.36	2.44	-

a) fu=0.04, Mw 427.40 g/mol B/P=0.83, Cmax from study A002-11

b) fu= 0.05, Mw413.8 g/mol

c) fu=0.07, Mw 399.4 g/mol

Cariprazine and DDCAR were shown to be inhibitors of P-gp in Caco-2 cells with IC50s of 2.1 µM and 12.2 µM respectively. Thus, a risk for a clinically relevant drug-drug interactions due to cariprazine Pgp-inhibition at the intestinal level cannot be excluded base on these data, whereas the risk for systemic inhibition of cariprazine is expected to be low. DCAR was not a P-gp inhibitor.

Cariprazine (5 -100 µM) did not demonstrate strong competitive inhibition of the P450s tested (CYP1A2, CYP2A6, CYP2C9, CYP2CI9 and CYP3A4); except a weak inhibitory effect on CYP2D6 with Ki values of 33.5-36 µM.

Using pre-incubation up to 30 min 200 µM cariprazine did not exhibit significant mechanism based inhibition in the CYP enzyme activities compared to the control incubations. Cariprazine, DCAR and DDCAR did not inhibit the CYP enzymes the concentration range tested (0.025 µM - 5 µM), or the inhibition was very weak even at the highest test concentration (less than 20%).

In the CYP induction study using human hepatocytes cariprazine showed less than 100% increase in CYP1A2, CYP2B6 and CYP3A4 mRNA at its 50- fold mean unbound Cmax concentration. The results showed over 100% increase of CYP3A4 mRNA at higher concentrations expected to occur in the intestinal compared to vehicle control, indicating that the risk for clinically significant induction of CYP3A in the intestine cannot be excluded. DCAR and DDCAR showed less than 100% increase in CYP1A2, CYP2B6 and CYP3A4 mRNA compared to vehicle control.

Based on *in vitro* studies it could be concluded that cariprazine, DCAR and DDCAR are not inhibitors of the transporters OAT1, OAT3, OCT2 OATP1B1 or 1B3.

Effects of other drugs on the pharmacokinetics of cariprazine

A DDI study with parallel group design administering 400 mg ketoconazole daily for 10 days together with 0.5-mg cariprazine increased cariprazine Cmax and AUC by 3.42- to 3.88-fold compared to cariprazine arm, the half-life was increased to 85 h compared to 67 h. The systemic exposure to DCAR was 65% to 68% of that in the cariprazine arm and the half-life was 74 h compared to 47 h. The exposure to DDCAR was increased with 1.4 fold and a slight prolongation of the half-life.

Based on *in vitro* studies it could be concluded that cariprazine, DCAR and DDCAR are neither OATP1B1 nor OATP1B3 substrates.

Dose proportionality and time dependencies

Cariprazine and its metabolites DCAR and DDCAR accumulate due to long half-life. The accumulation is predictable and additional time dependency is not evident. In a population PK analysis a shift in some distribution parameters were modelled for the first day of dosing but this has no importance for chronic dosing.

After repeated administration the exposure to cariprazine, DCAR and DDCAR is proportional to dose in the range from 1.5 mg to 12.5 mg. In the population PK analysis, apparent clearance for cariprazine, DCAR and DDCAR was independent of dose.

2.5.3. Pharmacodynamics

Mechanism of action

Cariprazine is an orally active and potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors and partial agonist at serotonin 5-HT1A receptors.

Primary and Secondary pharmacology

D3/D2 Receptor Occupancy

The receptor occupancy with positron emission tomography (PET) technique has been studied in three studies. Study RGH-188-003 has been performed in healthy volunteers and shown that after repeated

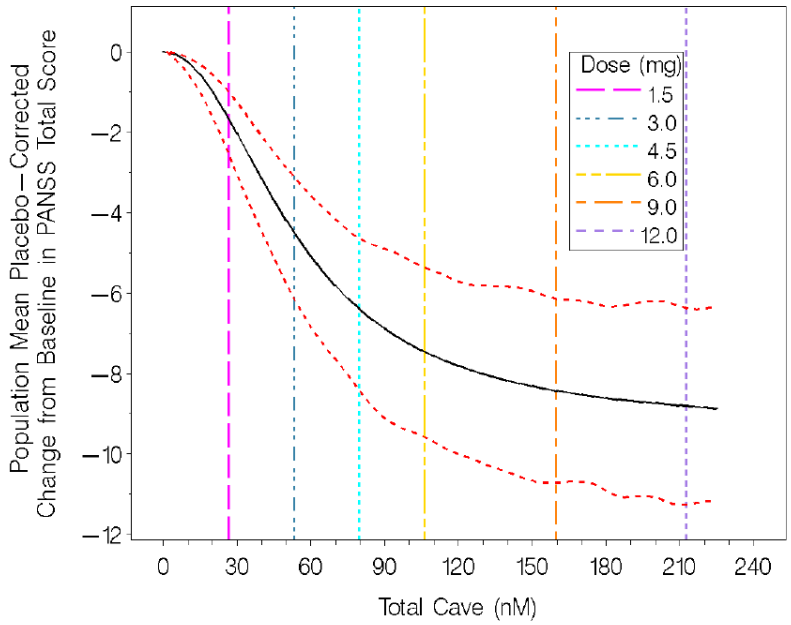
cariprazine dosing for 14 days (0.5 mg for 2 days and 1 mg for 12 days), regional occupancies in brain regions with known D3/D2 receptors were around 70%. In study RGH-MD-14 performed in patients with schizophrenia, maximum occupancy of ≥ 90% of the D3/D2 receptors at 3 mg/day; at a 1.5-mg/day dose, 76% to 86% occupancy of the D3/D2 receptors was observed across all brain regions including basal ganglia structures, i.e., caudate nucleus, putamen, and nucleus accumbens. In study RGH-PK-15, near complete receptor occupancy at both D2 and D3 receptor types was observed at 12 mg/day after 15 days of dosing for cariprazine and its metabolites in patients with schizophrenia. At the lowest dose of 1 mg/day, mean D3 and D2 occupancy was 76% (range 58% to 89%) and 45% (range 14% to 64%), respectively. At the dose of 3 mg/day, mean D3 and D2 occupancy was 92% (range 86% to 96%) and 79% (range 68% to 88%), respectively.

Effects on QT Interval

The effect of 9 mg/day and 18 mg/day cariprazine on cardiac repolarization was investigated in a multicenter, randomized, double-blind, placebo, and moxifloxacin-controlled, parallel-group study in patients with schizophrenia. There was no evidence that cariprazine results in statistically or clinically significant QTc prolongation following 9 mg/day, the highest tested dose in confirmatory trials to show efficacy, and a supratherapeutic dose (18 mg/day). No patients treated with cariprazine experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec in the study (RGH-MD-02). In a population PK-PD analysis, data from 11 studies were used to quantitatively evaluate the potential for QTcF prolongation by cariprazine plasma exposures. No clinically meaningful relationship between TOTAL cariprazine plasma concentrations and QTcF prolongation over the dose range of 0.5 to 21 mg/day was found (RGH-MS-02). A linear mixed effects model was developed to characterize and quantify the relationship between QTcF and time-matched predicted total concentration. Based on the model, QTcF is predicted to decrease by 1.2 msec for every 100 nM increase in total concentration. At the maximum total concentration of 431.6 nM observed in this patient population, QTcF is predicted to decrease by 5.18 msec. The placebo effect is a constant reduction of QTcF from baseline of 2.64 msec while on treatment.

Exposure-response modelling of PANSS

Pharmacokinetic/pharmacodynamic analyses were performed to characterize PANSS total score, PANSS negative score, and PANSS positive score in patients with schizophrenia. Models were developed to characterize the time-course of PANSS scores in the absence of treatment as well as exposure-response relationships for cariprazine and 2 metabolites, DCAR and DDCAR. A total of 10,327 observations from 1756 patients were included in the PK/PD dataset for these analyses. Of the 1756 patients included in these analyses, 370 were from the Phase 2 Study RGH-MD-03, 535 were from the Phase 2b Study RGH-MD-16, and 425 and 26 were, respectively, from the Phase 3 Studies RGH-MD-04 and RGH-MD-05. The final population PK/PD model for PANSS total scores was comprised of a Weibull time-course model to characterize placebo response and a sigmoid Emax model to describe the effect of combined cariprazine, DCAR, and DDCAR exposures (total Cave). The maximum pharmacologic effect of total Cave, corrected for placebo effect, was an 11.8% reduction in PANSS total score, however, this Emax was reduced to 3.11% in patients from Study RGH-MD-03. The Cave resulting in half-maximal effect (EC50) was estimated to 55 nM, corresponding to approximately 3 mg. The effect model included a Hill coefficient that was estimated to 2.11 indicating a steep exposure-response. Because of the steep exposure-response relationship, only minor incremental reductions in PANSS total scores are predicted for higher exposures. Comparing dose levels, the model predicted incremental improvement in total PANSS score is 172% (3 mg vs 1.5 mg) , 42% (4.5 mg vs 3 mg), 17% (6 mg vs 4.5 mg), 13% (9 mg vs 6 mg)and 5% (12 mg vs 9 mg). The figure below illustrates the modelled exposure response augmented with the expected steady state average plasma concentration (active moiety) for each dose level.



Exposure-response modeling of selected Adverse Events

Exposure-safety models were developed to relate the risk of experiencing selected TEAEs to individual measures of exposure, defined as the time-weighted total Cave for the dosing regimen of the patient on the date of the first occurrence of the AE or the time-weighted highest total Cave for patients not experiencing the event. The AEs evaluated included the following: Treatment-emergent occurrence of akathisia, EPS without akathisia or restlessness, nausea and/or vomiting and treatment-emergent occurrence of parkinsonism cluster. Logistic regression analysis was used to relate drug exposure and other covariate effects to dichotomous endpoints characterized with 2 levels of response (0 = not experiencing the event, and 1 = experiencing the event). A statistically significant relation between the probability of having a TEAE and exposure was not seen. However, a numerical increase in the probability of TEAEs was seen with increasing dose.

2.5.4. Discussion on clinical pharmacology

The pharmacological effect of cariprazine appears to be mediated by both parent compound and the metabolites DCAR and DDCAR. It can be agreed that the sum of cariprazine, DCAR and DDCAR is the active moiety.

Based on the fact that a [14C] labelled human mass balance study was not performed there remains a lack of full understanding of the existence of any human unique metabolite in plasma. The Applicant has described the investigation that has been performed to further examine the presence of any human unique metabolite. This includes three different investigations: a) six potential human-specific metabolites (whose structures were chosen on the basis of the potential biotransformation's of cariprazine by commonly observed metabolic pathways) were synthesized as standards and their presence was checked in human plasma by LC-HRMS and LC-MS/MS; b) further extracted ion chromatogram (EIC)-based data mining of the existing LC-MS/MS data obtained from plasma; c) theoretical modelling of potential metabolite pathways. None of these methods detected any hitherto unidentified human-specific metabolites. Although the probability that additional metabolites are formed in vivo in humans cannot be fully excluded, it is judged to be low.

It is generally established that a radioactive human mass balance should be a part of the drug development program in order to investigate the elimination pathways as well as to enable assessment of the relevance of non-clinical species with respect to formed human metabolites.

However, the applicant argued that administration of any radioactive dose of cariprazine is not possible due to the following reasons: a) the need for steady state conditions in patients; b) lack of assay sensitivity with a low radioactive dose (2 µCi); c) safety related issues prohibit administration of higher radioactive doses ranging from 20-100 µCi. Given the potential risk for lenticular changes and cataracts in human; i.e. potential serious toxicity to a sensitive organ, the request of a radioactive human mass balance study has been re-evaluated.

In this case, the elimination of cariprazine is investigated to an acceptable level based on the data generated using the unlabelled mass balance data and performed DDI studies. Undoubtedly, with data from the unlabelled mass balance study only, there remains a lack of full understanding in the preclinical bridge regarding human metabolites. Of the reasons described above, this uncertainty is considered low. Based on the fact that the available data indicate a low risk for the occurrence of a unique major human metabolite with a risk for a mutagenic or carcinogenic potential, request for a further mass balance evaluation is not considered justified due to that the risk of prolonged ocular human exposure to radiolabelled cariprazine cannot be neglected.

Cariprazine is considered to be a teratogen. A DDI study with an oral contraceptive is therefore needed and will be conducted post-approval. Adequate language in the SmPC awaiting the results of this study has been introduced.

The Applicant has conducted a DDI study between cariprazine and ketoconazole, a strong 3A4 inhibitor. However, based on those result, the Applicant should also investigate the interaction between cariprazine and a moderate CYP3A4 inhibitor to clarify whether a contraindication is required or if cariprazine could be used concomitantly with moderate CYP3A4 inhibitors, possibly using a reduced dose. In addition, the concomitant use of moderate CYP3A4 inhibitors with different CYP2D6 genotypes (PM, EM and UMs) should also be investigated. The study will be performed as PAM.

According to the Drug Interaction Guideline, information of the formation and elimination of active metabolites should be investigated if there are pharmacologically active metabolites estimated based on unbound systemic exposure whose in vitro activity contributes to ≥ 50% of the in vivo target pharmacological effect. This is true at least for DDCAR and possible also for DCAR. There is limited data which enzyme(s) that is/are involved in the elimination of DDCAR. Additional *in vitro* studies should be performed to investigate the contribution of other not so common CYP enzymes such as CYP2C8, CYP2J2 etc as well as other oxidative enzymes. This should be investigated as PAM.

2.5.5. Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- DDI study with oral contraceptives
- *in vitro* studies to investigate the contribution of CYP enzymes such as CYP2C8, CYP2J2 etc as well as other oxidative enzymes.
- Study exploring interaction between cariprazine and a moderate CYP3A4 inhibitor and the concomitant use of moderate CYP3A4 inhibitors with different CYP2D6 genotypes (PM, EM and UMs).

2.6. Clinical efficacy

The cariprazine program consisted of four 6-weeks, double-blind, placebo-controlled studies; one exploratory study and three confirmatory studies to assess efficacy in acute exacerbations of schizophrenia. The exploratory study (RGH-MD-03) used a flexible dose design. Two of the confirmatory studies (RGH-MD-04 and RHG-MD-16) used a fixed dose design with different cariprazine doses and aripiprazole 10 mg/day and risperidone 4 mg/day were included as active controls for assay sensitivity respectively. One study used a fixed/flexible dose design (RGH-MD-05).

To support the efficacy in maintaining antipsychotic effect, a relapse prevention study, (RGH-MD-06), using a randomized withdrawal design, was submitted. In addition, the Applicant conducted study (RGH-188-005) addressing the effects of cariprazine on predominant negative symptoms.

2.6.1. Dose response study

No formal dose-response studies were performed. The dose response relationship was primarily supported by the short-term clinical trials, mainly RGH-MD-03 and RGH-MD-16.

2.6.2. Main studies

RGH-MD-04

A double-blind, placebo and active-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia

Methods

This was a multinational, multicentre, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose study, to evaluate the efficacy, safety, and tolerability of cariprazine in patients with acute exacerbation of schizophrenia. A no-drug washout period of up to seven days followed by 6 weeks of double-blind treatment and a 2 week safety follow-up phase.

Patients who completed 6 weeks of double-blind treatment were eligible to enter a 52-week open-label extension study (RGH-MD-11). The patients not entering the extension phase were followed for 2 week safety follow-up phase, received treatment as usual and hospitalisation was optional.

Study Participants

Male or female inpatients 18-60 years of age, with a DSM-IV diagnosis of schizophrenia (disorganized, catatonic, paranoid, or undifferentiated) as determined by *Structured Clinical Interview for DSM-IV (SCID)* for a minimum of 1 year. Patients were required to have a PANSS-total score of at least 80 and a CGI-S of 4 at screening and at baseline. Patients were also required to have a rating of at least 4 (moderate) on at least 2 of the following 4 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness/persecution.

Treatments

After the screening phase, all randomized patients entered the double-blind 6 weeks treatment phase and were administered capsules cariprazine 3 and 6 mg, aripiprazole 10 mg or placebo.

Objectives

The objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine relative to placebo in patients with acute exacerbation of schizophrenia.

Outcomes/endpoints

The primary efficacy variable was change from baseline in the PANSS total score at week 6.

The secondary efficacy variable was change from baseline in the CGI-S score at week 6.

The additional efficacy variables were the change from baseline at week 6 for the following:

- NSA-16 total score and NSA-16 global negative symptoms rating
- CGI-I score
- PANSS positive and PANSS negative sub score
- PANSS responders (≥ 30% improvement in PANSS total score)
- SQLS-R4 total score, psychosocial score, and vitality score
- CDR Attention Battery power of attention score, continuity of attention score, cognitive reaction time, and reaction time variability
- Tests color trails test part I and part II

Sample size

The primary efficacy parameter was the change from baseline to Week 6 in PANSS total score. Adjusting for the multiple comparisons involving the 2 efficacy endpoints and 2 cariprazine dose groups by using the matched parallel gatekeeping procedure, a sample size of 150 patients per treatment group provided 88% power to detect an effect size (treatment group difference relative to pooled SD) of 0.42 for the primary efficacy parameter, at a 2-sided significance level of 5%, assuming a correlation coefficient of within-patient assessments of 0.7 and a dropout rate of 35%.

Randomisation and blinding

At the end of the screening phase, patients were randomized to one of four treatment groups in a 1:1:1:1 ratio: placebo, cariprazine 3 mg, cariprazine 6 mg/day, or aripiprazole 10 mg/day.

The investigational products were identical in appearance (size, shape, and color), taste, and packaging.

Statistical methods

The Intent-to-Treat (ITT) Population consisted of all patients in the Safety Population who had at least 1 post baseline assessment of the PANSS total score.

For the LOCF approach, only the post baseline total score of a parameter was imputed; the individual item scores were not carried forward. The baseline total score was carried forward only for the intermittent missing scores immediately after baseline. If all the post baseline values were missing, the baseline value was not carried forward.

The primary efficacy parameter was the change from baseline in PANSS total score at Week 6. The primary analysis was performed using an MMRM with treatment group, study center, visit, and treatment group by visit interaction as the fixed effects and the baseline value and baseline value-by-visit

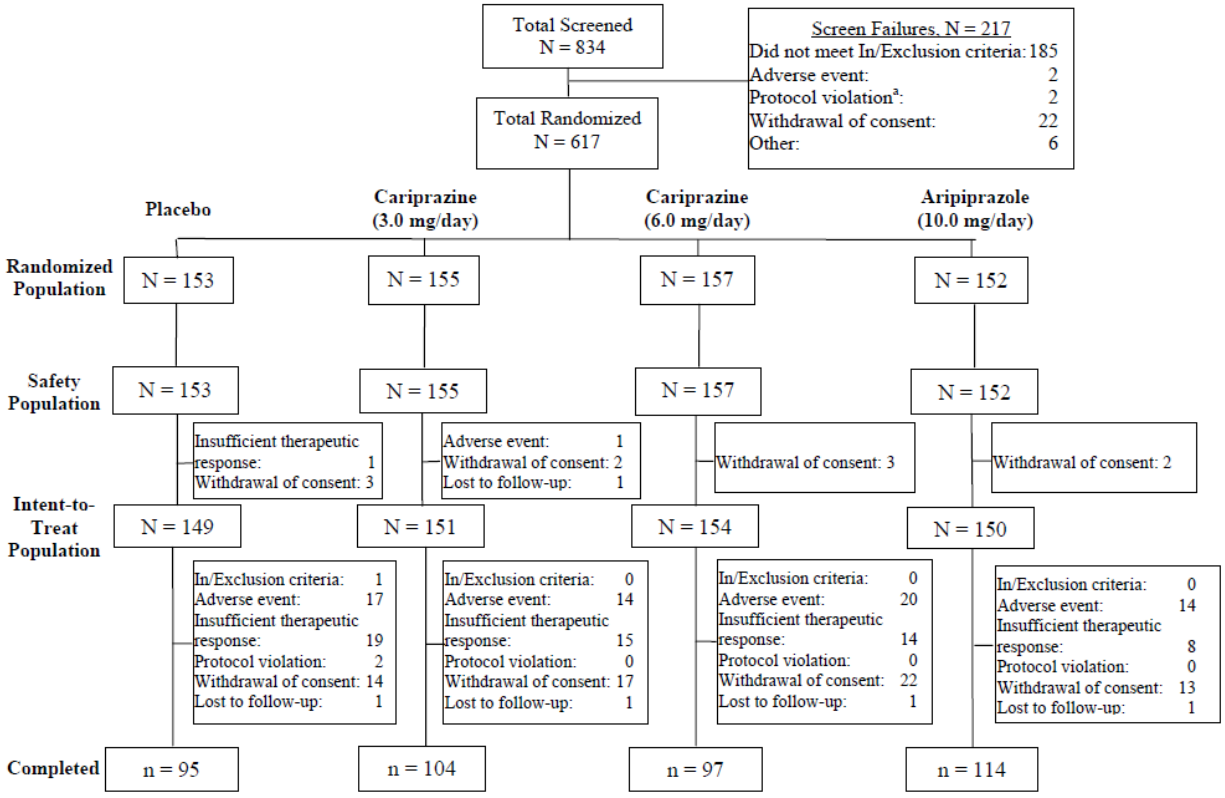
interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward and Roger, 1997) was used to estimate denominator degrees of freedom. This analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values.

To control the overall type I error rate for the multiple comparisons across the primary and the secondary hypotheses, a matched parallel gatekeeping procedure (Chen et al, 2005) was applied.

Analysis based on an analysis of covariance (ANCOVA) model, using the LOCF approach, was also performed. The ANCOVA model included treatment group and study center as factors and baseline PANSS total score as a covariate.

Results

Participant flow



Recruitment

A total of 617 patients were randomized and approximately two-thirds (66.5%) completed the study. The most frequent reasons for discontinuation were withdrawal of consent (12.3%), AE (10.7%), and insufficient therapeutic response (9.2%). There were no statistically significant differences between cariprazine 3 mg/day and placebo or cariprazine 6 mg/day and placebo in either overall discontinuation or in individual reasons for discontinuation.

Conduct of the study

This was a multi-centre study with 58 centres in total; 20 in the US, 12 in Romania, 14 in Russia and 12 in Ukraine. The first patient was enrolled 23 April 2010 and the last patient completed the last visit 20th of December 2011.

Baseline data

Demographic characteristics at baseline-safety population:

Characteristic	*Placebo (N = 153)*	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 152)*	*Total (N = 617)*
		3.0 (N = 155)	*6.0 (N = 157)*		
Age, years					
Mean ± SD	38.2 ± 11.3	37.9 ± 10.6	38.6 ± 10.6	39.3 ± 10.8	38.5 ± 10.8
Median (min, max)	37.0 (18, 60)	37.0 (18, 58)	38.0 (18, 60)	39.0 (18, 63)	38.0 (18, 63)
Sex, n (%)					
Male	97 (63.4)	99 (63.9)	100 (63.7)	94 (61.8)	390 (63.2)
Female	56 (36.6)	56 (36.1)	57 (36.3)	58 (38.2)	227 (36.8)
Race, n (%)					
White	93 (60.8)	102 (65.8)	101 (64.3)	99 (65.1)	395 (64.0)
All other races	48 (31.4)	36 (23.2)	39 (24.8)	37 (24.3)	160 (25.9)
Black or African-American	42 (27.5)	32 (20.6)	36 (22.9)	33 (21.7)	143 (23.2)
Asian	1 (0.7)	1 (0.6)	0	2 (1.3)	4 (0.6)
Native Hawaiian or other Pacific Islander	3 (2.0)	1 (0.6)	0	1 (0.7)	5 (0.8)
Other	2 (1.3)	2 (1.3)	3 (1.9)	1 (0.7)	8 (1.3)
Missing[a]	12 (7.8)	17 (11.0)	17 (10.8)	16 (10.5)	62 (10.0)
Ethnicity, n (%)					
Hispanic	3 (2.0)	2 (1.3)	5 (3.2)	2 (1.3)	12 (1.9)
Non-Hispanic	137 (89.5)	134 (86.5)	133 (84.7)	134 (88.2)	538 (87.2)
Missinga	13 (8.5)	19 (12.3)	19 (12.1)	16 (10.5)	67 (10.9)

a Data on race and ethnicity were not collected in Romania because of local regulations. However, 5 patients in Romania had race recorded as "Other" and 2 had race recorded as "White."

max = maximum; min = minimum; N = number of patients in the Safety Population; n = number of patients in the specified category.

Psychiatric history-safety population:

Characteristic	*Placebo (N = 153)*	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 152)*	*Total n (%) (N = 617)*
		3.0 (N = 155)	*6.0 (N = 157)*		
Schizophrenia subtype, n (%)					
Disorganized	3 (2.0)	0	1 (0.6)	1 (0.7)	5 (0.8)
Catatonic	0	1 (0.6)	0	1 (0.7)	2 (0.3)
Paranoid	140 (91.5)	148 (95.5)	149 (94.9)	143 (94.1)	580 (94.0)
Undifferentiated	10 (6.5)	6 (3.9)	7 (4.5)	7 (4.6)	30 (4.9)
Duration of schizophrenia, years[a]					
Mean ± SD	12.46 ± 9.65	12.37 ± 8.73	11.68 ± 9.02	12.40 ± 8.89	12.22 ± 9.06
Median (min, max)	10.37 (1.1, 41.7)	10.55 (1.0, 36.1)	9.65 (1.0, 43.8)	10.74 (1.1, 36.7)	10.29 (1.0, 43.8)
Number of previous psychiatric hospitalizations					
Mean ± SD	7.2 ± 9.4	7.3 ± 6.6	7.6 ± 7.2	7.5 ± 9.4	7.4 ± 8.2
Median (min, max)	5.0 (0, 99)	5.0 (0, 50)	5.0 (0, 45)	5.0 (0, 99)	5.0 (0, 99)
Suicide and violence history, n (%)					
Attempted suicide	25 (16.3)	35 (22.6)	29 (18.5)	32 (21.1)	121 (19.6)
Violent	16 (10.5)	16 (10.3)	13 (8.3)	14 (9.2)	59 (9.6)

a Duration of Schizophrenia (years) = (date of informed consent - onset date of original diagnosis of schizophrenia + 1)/365.25

max = maximum; min = minimum; N = number of patients in the Safety Population; n = number of patients in the specified category.

Baseline efficacy variables ITT-population:

Efficacy Parameter	*Placebo (N = 149)*	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 150)*	*p-value*
		3.0 (N = 151)	*6.0 (N = 154)*		
PANSS Total Score					
Mean ± SD	96.5 ± 9.1	96.1 ± 8.7	95.7 ± 9.4	95.6 ± 9.0	0.7515
PANSS Positive Score					
Mean ± SD	24.6 ± 3.4	25.3 ± 3.7	24.6 ± 3.4	24.7 ± 3.5	0.1710
PANSS Negative Score					
Mean ± SD	25.0 ± 4.3	24.0 ± 4.2	24.2 ± 4.2	24.3 ± 4.5	0.1483
CGI-S Score					
Mean ± SD	4.8 ± 0.6	4.9 ± 0.6	4.8 ± 0.6	4.8 ± 0.6	0.1730
NSA-16 Total Score					
Mean ± SD	56.2 ± 11.3	52.8 ± 12.2	54.4 ± 11.6	54.2 ± 11.1	0.0245
NSA Global Negative Symptom Rating					
Mean ± SD	4.3 ± 0.9	4.0 ± 1.0	4.1 ± 0.9	4.1 ± 1.0	0.0738
SQLS-R4 Total Score					
Mean ± SD	56.6 ± 21.5	54.4 ± 21.5	56.2 ± 22.6	58.4 ± 21.8	0.2993
SQLS-R4 Psychosocial Score					
Mean ± SD	32.9 ± 14.4	31.4 ± 14.3	33.0 ± 15.6	34.4 ± 14.4	0.2244
SQLS-R4 Vitality Score					
Mean ± SD	23.7 ± 8.6	23.0 ± 8.6	23.1 ± 8.5	24.0 ± 8.9	0.5714

Note: For continuous variables, p-values are from an analysis of variance model with treatment group and pooled study center as factors. For categorical variables, p-values are from Cochran-Mantel-Haenszel test controlling for study center.

CGI-S = Clinical Global Impressions–Severity; max = maximum; min = minimum; N = number of patients in the Safety Population; NSA-16 = 16-Item Negative Symptom Assessment; PANSS = Positive and Negative Syndrome Scale; SQLS-R4 = Schizophrenia Quality of Life Scale Revision 4.

Numbers analysed

A total of 617 patients were randomized and approximately two-thirds (66.5%) completed the study. The most frequent reasons for discontinuation were withdrawal of consent (12.3%), AE (10.7%), and insufficient therapeutic response (9.2%). There were no statistically significant differences between the groups in either overall discontinuation or in individual reasons for discontinuation.

Outcomes and estimation

Primary efficacy endpoint

The primary efficacy parameter was the change from baseline to week 6 in the PANSS-T score using a MMRM approach. A statistically greater change in the PANSS-T score was demonstrated for each cariprazine treatment group compare to the placebo group with a larger treatment difference observed for the cariprazine 6 mg/day treatment group. The LOCF analyses also indicated the same statistically

significant differences. The change in the PANSS-T score was also statistically significant relative to placebo for the aripiprazole treatment group.

Table 2. Change from baseline to week 6 in the PANSS-T score (MMRM), ITT population:

	Placebo (N = 149)	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 150)*
		3.0 (N = 151)	*6.0 (N = 154)*	
Baseline PANSS total score, mean ± SD	96.5 ± 9.1	96.1 ± 8.7	95.7 ± 9.4	95.6 ± 9.0
Change at Week 6				
LS mean (SE)	−14.3 (1.5)	−20.2 (1.5)	−23.0 (1.5)	−21.2 (1.4)
LSMD (95% CI) versus placebo	—	−6.0 (−10.1, −1.9)	−8.8 (−12.9, −4.7)	−7.0 (−11.0, −2.9)
p–value[a]	—	0.0044	< 0.0001	0.0008
Adjusted p–value[b]	—	0.0044	< 0.0001	—

a P-values are from an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within–patient scores.

b Adjusted P-values = adjusted by matched parallel gatekeeping procedure.

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the Intent-to-Treat Population; PANSS = Positive and Negative Syndrome Scale.

Table 3. Sensitivity analysis: Change from baseline to week 6 in the PANSS-T score (LOCF) ITT population:

	Placebo (N = 149)	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 150)*
		3.0 (N = 151)	*6.0 (N = 154)*	
Baseline PANSS total score, mean ± SD	96.5 ± 9.1	96.1 ± 8.7	95.7 ± 9.4	95.6 ± 9.0
Change at Week 6				
LS mean (SE)	−11.0 (1.4)	−16.4 (1.4)	−18.9 (1.4)	−18.8 (1.4)
LSMD (95% CI) versus placebo	—	−5.4 (−9.3, −1.4)	−7.9 (−11.8, −4.0)	−7.7 (−11.7, −3.8)
p–value[a]	—	0.0078	< 0.0001	0.0001

a P-values are from an ANCOVA model with treatment group and pooled study center as factors and the baseline value as covariate.

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; N = number of patients in the Intent-to-Treat Population; PANSS = Positive and Negative Syndrome Scale.

Secondary efficacy endpoints

The secondary efficacy parameter was the change from baseline at week 6 in the CGI-S score analysed using MMRM approach showing a change statistically significant greater than placebo for all the treatment groups. It was also analysed using a LOCF with a similar outcome as the primary analysis.

Table 4. Change from baseline at week 6 in the CGI-S score-ITT population:

	Placebo (N = 149)	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 150)*
		3.0 (N = 151)	*6.0 (N = 154)*	
Baseline CGI-S score, mean ± SD	4.8 ± 0.6	4.9 ± 0.6	4.8 ± 0.6	4.8 ± 0.6
MMRM				
Change at Week 6				
LS mean (SE)	–1.0 (0.1)	–1.4 (0.1)	–1.5 (0.1)	–1.4 (0.1)
LSMD (95% CI) versus placebo	—	–0.4 (–0.6, –0.2)	–0.5 (–0.7, –0.3)	–0.4 (–0.6, –0.2)
p–value[a]	—	0.0004	< 0.0001	0.0001
Adjusted p–value[b]	—	0.0044	< 0.0001	—

	Placebo (N = 149)	*Cariprazine, mg/day*		*Aripiprazole 10.0 mg/day (N = 150)*
		3.0 (N = 151)	*6.0 (N = 154)*	
LOCF				
Change at Week 6				
LS mean (SE)	–0.7 (0.1)	–1.1 (0.1)	–1.2 (0.1)	–1.2 (0.1)
LSMD (95% CI) versus placebo	—	–0.4 (–0.6, –0.2)	–0.5 (–0.7, –0.2)	–0.5 (–0.7, –0.3)
p–value[c]	—	0.0005	< 0.0001	< 0.0001

a P-values are from an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within–patient scores.

b Adjusted p-values = adjusted by matched parallel gatekeeping procedure.

c P-values are from an ANCOVA model with treatment group and pooled study center as factors and the baseline value as covariate.

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the Intent-to-Treat Population.

Ancillary analyses

The results of the additional analyses of NSA-16 total score, CGI-I score, PANSS positive and negative scores and the NSA-16 global negative symptoms rating, SQLS-R4 total score, SQLS-R4 psychosocial score and SQLS-R4 vitality score were all consistent with the primary and secondary efficacy analyses, with statistically significant improvements relative to placebo seen for all treatment groups. In the CDR attention battery and colour trails test scores some improvements were seen in the cariprazine group

A higher percentage of patients in the active treatment groups, cariprazine 3.0 and 6.0, (24.5% and 31.8% respectively) and aripriprazole (30.0%) achieved a 30% or greater improvement in PANSS total score than patients receiving placebo (19.5%). Statistically significant differences from placebo were seen for the cariprazine 6 mg/day and aripiprazole treatments groups.

RGH-MD-05

A double-blind placebo-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia

Methods

This was a multinational, multicentre, randomized, double-blind, placebo-controlled, parallel-group, fixed/flexible-dose study, to evaluate the efficacy, safety, and tolerability of cariprazine in patients with acute exacerbation of schizophrenia. This study was 9 weeks in duration and consisted of a no-drug washout phase of up to seven days followed by 6 weeks of double-blind treatment and a 2-week safety follow-up phase.

Study Participants

Male or female inpatients 18-60 years of age, with a DSM-IV diagnosis of schizophrenia (disorganized, catatonic, paranoid, or undifferentiated) as determined by Structured Clinical Interview for DSM-IV (SCID) for a minimum of 1 year. Patients were required to have a PANSS-T score of at least 80 and a Clinical Global Impression of Severity (CGI-S) of 4 at screening and at baseline. Patients were also required to have a rating of at least 4 (moderate) on at least 2 of the following 4 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness/persecution

Treatments

After the washout period, all randomized patients entered the 6 week double-blind treatment period, during which they were administered cariprazine (3.0 mg or 6.0 mg/day) or placebo as a single daily oral dose. All patients were given one capsule for weeks 1 and 2, from week 3 to week 6 two capsules were administered if response was not adequate and no tolerability problems were found. Patients randomized to the low-dose cariprazine group (3-6 mg/day) received 4.5 mg/day for 2 days and 6 mg/day thereafter. Patients randomized to the high-dose cariprazine group (6-9 mg/day) received 7.5 mg/day for 2 days and 9 mg/day thereafter. Patients not warranted a dose increase continued taking 1 capsule per day. Doses were fixed from the end of week 3 to 6.

Objectives

The objective of this study was to evaluate the safety, efficacy and tolerability of cariprazine relative to placebo in patients with acute exacerbation of schizophrenia.

Outcomes/endpoints

The primary efficacy variable was change from baseline in the PANSS total score at week 6.

The secondary efficacy variable was change from baseline in the CGI-S score at week 6.

The additional efficacy variables were the change from baseline at week 6 for the following:

- NSA-16 total score and global negative symptoms rating
- CGI-I score at week 6
- PANSS positive and PANSS negative score
- SQLS-R4
- PANSS responders
- CDR attention tests and color trails test

Sample size

The primary efficacy parameter was the change from baseline to Week 6 in PANSS total score. Adjusting for the multiple comparisons involving the 2 efficacy endpoints and 2 cariprazine dose groups by using the matched parallel gatekeeping procedure, a sample size of 150 patients per treatment group provided 88% power to detect an effect size (treatment group difference relative to pooled SD) of 0.42 for the primary efficacy parameter, at a 2-sided significance level of 5%, assuming a correlation coefficient of within-patient assessments of 0.7 and a dropout rate of 35%.

Randomisation and blinding

At the end of the screening phase, patients were randomized to one of three treatment groups in a 1:1:1 ratio: placebo, cariprazine 3 -6 mg, or cariprazine 6-9 mg.

The investigational products were identical in appearance (size, shape, and color), taste, and packaging.

Statistical methods

The Intent-to-Treat (ITT) Population consisted of all patients in the Safety Population who had at least 1 postbaseline assessment of the PANSS total score.

For the LOCF approach, only the postbaseline total score of a parameter was imputed; the individual item scores were not carried forward. The baseline total score was carried forward only for the intermittent missing scores immediately after baseline. If all the postbaseline values were missing, the baseline value was not carried forward.

The primary efficacy parameter was the change from baseline in PANSS total score at Week 6. The primary analysis was performed using an MMRM with treatment group, study center, visit, and treatment group by visit interaction as the fixed effects and the baseline value and baseline value-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward and Roger, 1997) was used to estimate denominator degrees of freedom. This analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values.

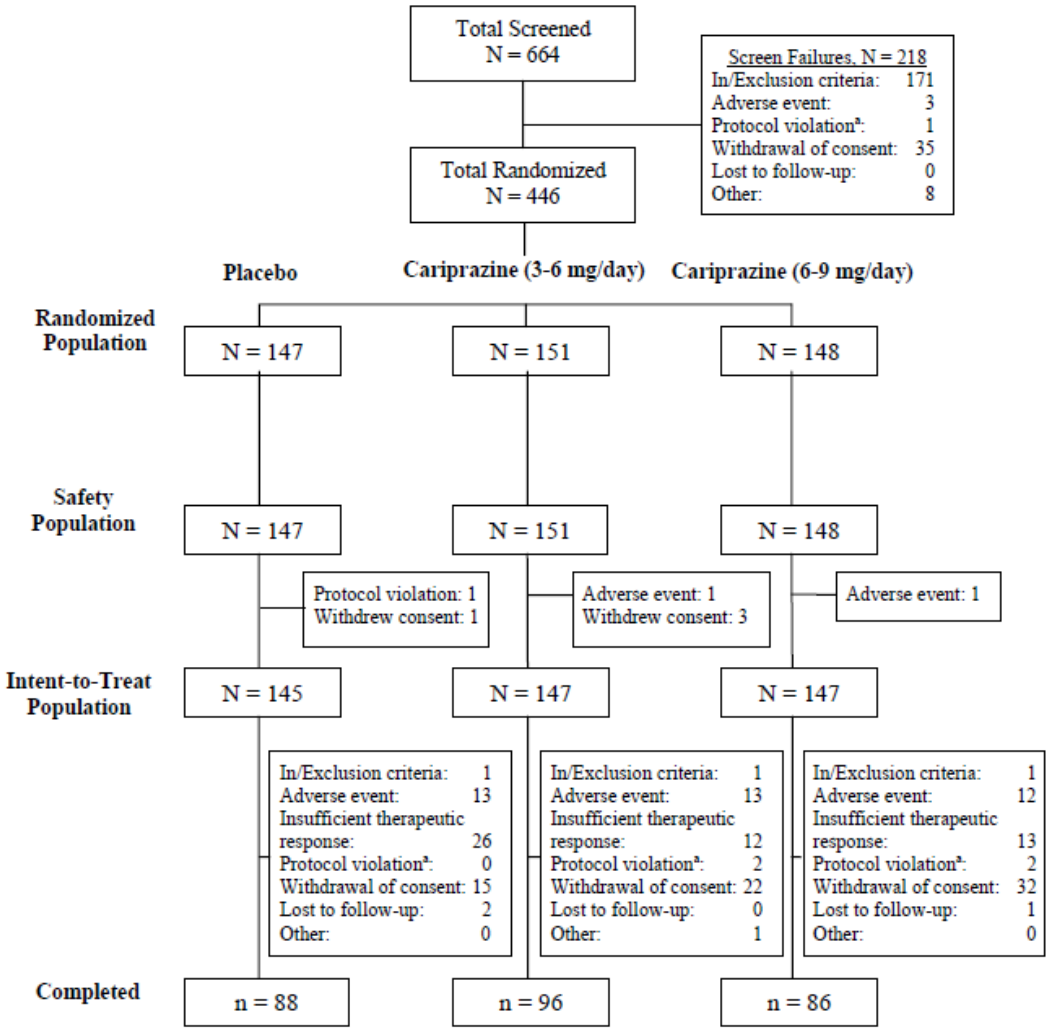
To control the overall type I error rate for the multiple comparisons across the primary and the secondary hypotheses, a matched parallel gatekeeping procedure (Chen et al, 2005) was applied.

A sensitivity analysis using a pattern-mixture model (PMM) based on non-future dependent missing value restrictions (Kenward et al, 2003) was performed to assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption.

Analysis based on an analysis of covariance (ANCOVA) model, using the LOCF approach, was also performed. The ANCOVA model included treatment group and study center as factors and baseline PANSS total score as a covariate.

Results

Participant flow



Note: One patient (first enrollment PID 0500503, second enrollment PID 0480521) was enrolled twice in the study. Only data from the first enrollment period are included. All patients from Study Center 504 and 043 are excluded due to GCP violation; their data are included in the listings for full disclosure.

a Protocol violation was a reason for premature discontinuation, as indicated by the Investigator on the Study Termination Record of the eCRF.

eCRF = electronic case report form; GCP = good clinical practice; N = number of patients in the specified population; n = number of patients in the specified category; PID = patient identification.

Recruitment

A total of 446 patients were randomised and approximately 60% completed the study. The most frequent reasons for discontinuation were withdrawal of consent (16.4%), insufficient response (11.4%), and AEs (9.0%). Significantly more patients in the placebo group discontinued because of insufficient therapeutic response compared to the cariprazine groups. Significantly more patients in the cariprazine 6-9 mg/day group compared with the placebo group discontinued due to withdrawal of consent.

Conduct of the study

There were 41 centres in total; 15 in the US, 4 in Colombia, 19 in India, and 3 in South Africa.

Two study centres were identified to have GCP violations in the study conduct and these data were not included in the efficacy or safety analyses. However, sensitivity analyses were performed with these study centres included.

Baseline data

Table 5. Demographic characteristics at baseline-safety population:

Characteristic	*Placebo (N = 147)*	*Cariprazine 3-6 mg/day (N = 151)*	*Cariprazine 6-9 mg/day (N = 148)*	*Total (N = 446)*
Age, years				
Mean ± SD	36.7 ± 11.3	36.6 ± 10.5	35.5 ± 9.3	36.3 ± 10.4
Median (min, max)	35.0 (18, 60)	36.0 (18, 60)	34.5 (18, 57)	35.0 (18, 60)
Sex, n (%)				
Male	110 (74.8)	118 (78.1)	113 (76.4)	341 (76.5)
Female	37 (25.2)	33 (21.9)	35 (23.6)	105 (23.5)
Race, n (%)				
White	26 (17.7)	28 (18.5)	30 (20.3)	84 (18.8)
All other races	121 (82.3)	123 (81.5)	118 (79.7)	362 (81.2)
Black or African American	51 (34.7)	56 (37.1)	53 (35.8)	160 (35.9)
Asian	56 (38.1)	56 (37.1)	56 (37.8)	168 (37.7)
American Indian or Alaska Native	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.7)	0	2 (1.4)	3 (0.7)
Other	12 (8.2)	10 (6.6)	6 (4.1)	28 (6.3)
Ethnicity, n (%)				
Hispanic	23 (15.6)	24 (15.9)	27 (18.2)	74 (16.6)
Non-Hispanic	124 (84.4)	127 (84.1)	121 (81.8)	372 (83.4)

max = maximum; min = minimum; N = number of patients in the Safety Population; n (%) = number (percentage) of patients in the specified category.

There were no statistically significant differences among the treatment groups with respect to demographics, physical characteristics. The most common conditions present at baseline were psychiatric disorders and headache which were reported equally by patients in each treatment group.

Most patients had paranoid schizophrenia. The treatment groups were matched with regard to psychiatric history. About 13% of patients had history of substance-related disorders.

Table 6. Psychiatric history-safety population:

	Placebo (N = 147)	*Cariprazine 3-6 mg/day (N = 151)*	*Cariprazine 6-9 mg/day (N = 148)*	*Total (N = 446)*
Schizophrenia subtype, n (%)				
Disorganized	5 (3.4)	9 (6.0)	8 (5.4)	22 (4.9)
Catatonic	1 (0.7)	0	0	1 (0.2)
Paranoid	117 (79.6)	125 (82.8)	120 (81.1)	362 (81.2)
Undifferentiated	24 (16.3)	17 (11.3)	20 (13.5)	61 (13.7)
Duration of schizophrenia, y[a]				
Mean ± SD	10.98 ± 10.23	11.29 ± 10.35	9.94 ± 8.18	10.74 ± 9.64
Median (min, max)	7.12 (1.1, 40)	7.37 (0.7, 42)	7.97 (1.1, 40)	7.60 (0.7, 42)
Number of previous psychiatric hospitalizations				
Mean ± SD	3.5 ± 4.4	4.8 ± 6.4	3.9 ± 5.2	4.1 ± 5.4
Median (min, max)	2.0 (0, 25)	2.0 (0, 40)	2.0 (0, 22)	2.0 (0, 40)
Suicide and violence history, n (%)				
Attempted suicide	21 (14.3)	30 (19.9)	20 (13.5)	71 (15.9)
Violent	17 (11.6)	10 (6.6)	14 (9.5)	41 (9.2)

a Duration of schizophrenia (y) = (date of informed consent - onset date of original diagnosis of schizophrenia + 1) /365.25.

max = maximum; min = minimum; N = number of patients in the Safety Population; n (%) = number (percentage) of patients in a specific category; y = year(s).

Table 7. Baseline efficacy variables-ITT population

Efficacy Parameters	*Placebo (N = 145)*	*Cariprazine 3-6 mg/day (N = 147)*	*Cariprazine 6-9 mg/day (N = 151)*	*p-value*
PANSS Total Score				
Mean ± SD	96.6 ± 9.3	96.3 ± 9.3	96.3 ± 9.0	0.9626
PANSS Positive Score				
Mean ± SD	26.3 ± 3.6	26.0 ± 3.3	26.5 ± 3.6	0.4715
PANSS Negative Score				
Mean ± SD	24.1 ± 4.2	23.9 ± 4.3	24.1 ± 4.0	0.8466
CGI-S Score				
Mean ± SD	4.9 ± 0.7	4.8 ± 0.7	4.9 ± 0.7	0.6825
NSA-16 Total Score				
Mean ± SD	54.2 ± 9.6	54.7 ± 11.6	55.3 ± 10.8	0.6303
NSA Global Negative Symptoms Rating				
Mean ± SD	4.0 ± 0.8	4.0 ± 1.0	4.0 ± 0.9	0.9925
SQLS-R4 Total Score				
Mean ± SD	61.3 ± 22.7	60.1 ± 20.3	59.3 ± 19.4	0.8275
SQLS-R4 Psychosocial Score				
Mean ± SD	37.5 ± 15.7	36.2 ± 13.6	36.4 ± 13.7	0.8755
SQLS-R4 Vitality Score				
Mean ± SD	23.8 ± 8.1	23.9 ± 8.1	22.8 ± 7.1	0.4218

Note: For continuous variables, p-values are from an ANOVA model with treatment group and pooled study center as factors. For categorical variables, p-values are from Cochran-Mantel-Haenszel test controlling for study center.

ANOVA = analysis of variance; CGI-S = Clinical Global Impressions–Severity; max = maximum; min = minimum; N = number of patients in the Intent-to-Treat Population; NSA = Negative Symptom Assessment; NSA-16 = 16-Item Negative Symptom Assessment; PANSS = Positive and Negative Syndrome Scale; SQLS-R4 = Schizophrenia Quality of Life Scale Revision 4.

There were no imbalances between the groups with regard to baseline efficacy parameters. Most patients (76.5%) received concomitant medications during the double-blind treatment phase. The use of anti-Parkinson drugs and beta-blockers was much higher in the cariprazine 3-6 and 6-9 mg/day groups than in the placebo group. The most commonly used concomitant medications were psycholeptics, used most frequently in the cariprazine 6-9 mg/day group. Rescue medication was used similarly among the treatment groups.

Numbers analysed

A total of 446 patients were randomised and approximately 60% completed the study. The most frequent reasons for discontinuation were withdrawal of consent (16.4%), insufficient response (11.4%), and AEs (9.0%). Significantly more patients in the placebo group discontinued because of insufficient therapeutic response compared to the cariprazine groups. Significantly more patients in the cariprazine 6-9 mg/day group compared with the placebo group discontinued due to withdrawal of consent.

Outcomes and estimation

The primary efficacy endpoint

The primary efficacy parameter was the change from baseline to week 6 in the PANSS total score using an MMRM analysis. Relative to placebo group, the change in each cariprazine group was statistically significant.

Table 8. Change form baseline to week 6 in PANSS total score (MMRM) -ITT population

	Placebo (N = 145)	*Cariprazine 3-6 mg/day (N = 147)*	*Cariprazine 6-9 mg/day (N = 147)*
Baseline PANSS total score, Mean ± SD	96.6 ± 9.3	96.3 ± 9.3	96.3 ± 9.0
Change at Week 6			
LS mean (SE)	–16.0 (1.6)	–22.8 (1.6)	–25.9 (1.7)
LSMD vs placebo (95% CI)	—	–6.8 (–11.3, –2.4)	–9.9 (–14.5, –5.3)
p-value[a]	—	0.0029	< 0.0001
Adjusted p-value[b]	—	0.0029	< 0.0001

a P-values are from an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within–patient scores.

b Adjusted p-values = adjusted by matched parallel gatekeeping procedure.

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the Intent-to-Treat Population; PANSS = Positive and Negative Syndrome Scale; SE = standard error of the LS mean.

Similar results were observed using the LOCF approach.

Table 9. Change from baseline to week 6 in the PANSS-T score (LOCF)-ITT population

	Placebo (N = 145)	*Cariprazine 3-6 mg/day (N = 147)*	*Cariprazine 6-9 mg/day (N = 147)*
Baseline PANSS total score, Mean ± SD	96.6 ± 9.3	96.3 ± 9.3	96.3 ± 9.0
Change at Week 6			
LS mean (SE)	–12.3 (1.5)	–18.6 (1.5)	–20.2 (1.5)
LSMD vs placebo (95% CI)	—	–6.3 (–10.2, –2.4)	–8.0 (–11.9, –4.0)
p-value[a]	—	0.0016	< 0.0001

a P-values are from an ANCOVA model with treatment group and pooled study center as factors and the baseline value as covariate.

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; LOCF = last observation carried forward; LSMD = least squares mean difference; N = number of patients in the Intent-to-Treat Population; PANSS = Positive and Negative Syndrome Scale; SE = standard error of the LS mean.

The secondary efficacy endpoint

The secondary efficacy parameter was the change from baseline to week 6 in the CGI-S score and was analysed using an MMRM. An ANCOVA model based on the LOCF approach was also used. Relative to placebo, the change in each cariprazine group was statistically significant using both approaches.

Table 10. Change from baseline to week 6 in CGI-S score-ITT-population

	Placebo (N = 145)	*Cariprazine 3-6 mg/day (N = 147)*	*Cariprazine 6-9 mg/day (N = 147)*
Baseline CGI-S score, Mean ± SD	4.9 ± 0.7	4.8 ± 0.7	4.9 ± 0.7
MMRM			
Change at Week 6			
LS mean (SE)	–1.0 (0.1)	–1.4 (0.1)	–1.6 (0.1)
LSMD (95% CI)	—	–0.3 (–0.6, –0.1)	–0.5 (–0.8, –0.3)
p-value[a]	—	0.0115	< 0.0001
Adjusted p-value[b]	—	0.0115	0.0002
LOCF			
Change at Week 6			
LS mean (SE)	–0.7 (0.1)	–1.0 (0.1)	–1.2 (0.1)
LSMD (95% CI)	—	–0.3 (–0.5, –0.0)	–0.4 (–0.7, –0.2)
p-value[c]	—	0.0199	0.0003

a P-values are from an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores.

b Adjusted p-values = adjusted by matched parallel gatekeeping procedure.

c P-values are from an ANCOVA model with treatment group and pooled study center as factors and the baseline value as covariate.

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the Intent-to-Treat Population; SE = standard error of the LS mean.

Ancillary analyses

Additional efficacy parameters were the change form baseline to week 6 in the PANSS positive and negative score, NSA-16 total score, NSA global negative symptoms rating, the CGI-I at week 6 and the percentage of PANSS responders at week 6. In addition, the change from baseline to week 6 in SQLS-R4 total, psychological and vitality scores, CDR attention battery tests and color traits test, were considered additional parameters. Compared to placebo, significant differences were observed using the MMRM approach in the changes to week 6 in PANSS positive and negative scores, CGI-I score, and NSA-16 total score. Similar results were observed using the ANCOVA with LOCF approach.

Compared to placebo, significant differences were observed in the changes to week 6 in SQLS-R4 total score and SLS-R4 vitality score for the cariprazine group 3-6 mg only. Compared to placebo, there were no significant differences in either of the cariprazine groups in the changes to week 6 in any of the CDR or CTT scores.

RGH-MD-16

Evaluation of the safety and efficacy of RGH-188 in the acute exacerbation of schizophrenia

Methods

This was a multinational, multicentre, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose study, to evaluate the efficacy, safety, and tolerability of cariprazine in patients with acute exacerbation of schizophrenia. This study was 9 weeks in duration and consisted of a no-drug washout period of up to seven days followed by 6 weeks of double-blind treatment and a 2 week safety follow-up phase.

Study Participants

Male or female inpatients 18-60 years of age, with a DSM-IV diagnosis of schizophrenia (disorganized, catatonic, paranoid, or undifferentiated) as determined by *Structured Clinical Interview for DSM-IV (SCID)* for a minimum of 1 year. Patients were required to have a PANSS-T score of at least 80 and a Clinical Global Impression of Severity (CGI-S) of 4 at screening and at baseline. Patients were also required to have a rating of at least 4 (moderate) on at least 2 of the following 4 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness/persecution.

Treatments

After the washout period, all randomized patients entered the 6 week double-blind treatment period, during which they were administered cariprazine (1.5 mg, 3.0 mg or 4.5 mg/day), risperidone (4.0 mg/day) or placebo as a single daily oral dose.

Objectives

The objective of this study was to evaluate the safety, efficacy and tolerability of RGh-188 (cariprazine) relative to placebo in patients with acute exacerbation of schizophrenia.

Outcomes/endpoints

The primary efficacy variable was change from baseline in the PANSS total score at week 6.

The secondary efficacy variable was change from baseline in the CGI-S score at week 6.

The additional efficacy variables were the change from baseline at week 6 for the following:

- NSA-16 total score and NSA-16 global negative symptoms rating
- CGI-I score
- PANSS positive and PANSS negative score
- PANSS responders (≥ 30% improvement in PANSS total score)

Sample size

The primary efficacy variable was the change from baseline (Visit 2) to Week 6 in the PANSS total score using the LOCF approach. Adjusting for multiple comparisons of 3 cariprazine treatment groups against placebo, a sample size of approximately 135 patients in each of the 4 treatment groups was determined sufficient to provide at least 80% power to detect an effect size (treatment group difference relative to pooled standard deviation) of 0.4.

Randomisation and blinding

At the end of the screening phase, patients were randomized to one of five treatment groups in a 1:1:1:1:1 ratio: placebo, cariprazine 1.5 mg/d, cariprazine 3.0 mg/d, cariprazine 4.5 mg/d or risperidone 4.0 mg/d.

The investigational products were identical in appearance (size, shape, and color), taste, and packaging.

Statistical methods

The Intent-to-Treat (ITT) Population consisted of all patients in the Safety Population who had at least one postbaseline assessment of the primary efficacy parameter, the PANSS total score.

The change from baseline (Visit 2) to Week 6 in PANSS total score was used as the primary efficacy parameter. The primary analysis was performed using the LOCF approach.

Between-treatment group comparisons were performed by means of an analysis of covariance (ANCOVA) model with treatment group and study center as factors and the baseline PANSS total score as the covariate. To control the overall type I error for comparisons of 3 doses of RGH-188 with placebo, the following sequential multiple-comparison procedure was used.

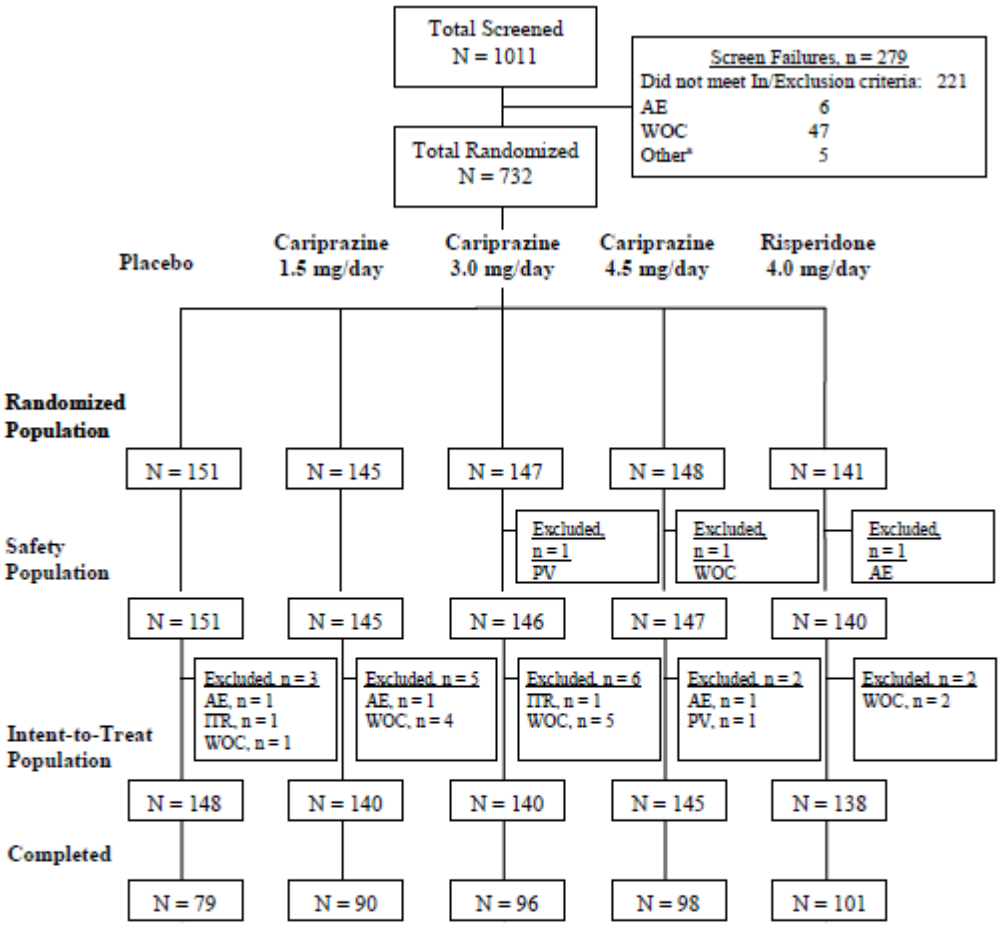
Step 1: The average effect of the 3.0-mg and 4.5-mg doses was compared with that of placebo. If the global test was significant at the 2-sided significance level of 0.05, then Step 2 was performed; otherwise, the analysis was stopped here.

Step 2: Each effect of the 3.0-mg and 4.5-mg doses were compared with that of placebo at the 2-sided significance level of 0.05. If both tests for the 3.0-mg and 4.5-mg groups were statistically significant at the 2-sided significance level of 0.05, Step 3 was performed; otherwise the analysis was stopped here.

Step 3: The effect of the 1.5-mg dose was compared with that of placebo at the 2-sided significance level of 0.05.
In addition, 2 sensitivity analyses, both using the OC approach, were performed on the primary efficacy parameter. For the first analysis, between-treatment group comparisons at Week 6 were performed using the same ANCOVA model as described above; however, only observed cases at Week 6 were used in the analysis. For the second analysis, between-treatment group comparisons at Week 6 were performed using a mixed-effects model for repeated measures (MMRM) with treatment group, study center, visit, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline-by-visit interaction as the covariates. The Kenward-Roger approximation was used to estimate denominator degrees of freedom (Kenward and Roger, 1997). An unstructured covariance matrix was used to model the covariance of within-patient scores. These analyses were performed based on all postbaseline scores using only the observed cases without imputation of missing values.

Results

Participant flow



Note: The Screened Population consisted of all patients who had a Visit 1, received a screening number, and signed the informed consent form.

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 of the PANSS total score (primary efficacy parameter).

a Other reasons were: abnormal clinical laboratory values (2 patients), inability to collect clinical laboratory assessments (2 patients) and the unavailability of the rater (1 patient).

AE = adverse event; ITR = insufficient therapeutic response; ITT = intent-to-treat; PANSS = Positive and Negative Syndrome Scale; PV = protocol violation; WOC = withdrawal of consent.

Recruitment

The first patient was enrolled 06 June 2008 and the last patient completed the last visit 25 August 2009.

Conduct of the study

This was a multi-centre study with 65 centres in total; 18 in the US, 16 in India, 15 in Russia, 11 in Ukraine and 5 in Malaysia.

Baseline data

Table 11. Demographic characteristics at baseline-safety population

Characteristic	*Placebo (N = 151)*	*Cariprazine, mg/day*			*Risperidone 4.0 mg/day (N = 140)*	*Total (N = 729)*
		1.5 (N = 145)	*3.0 (N = 146)*	*4.5 (N = 147)*		
Age, y						
Mean ± SD	36.0 ± 10.8	36.8 ± 9.6	37.1 ± 10.4	35.8 ± 10.8	36.5 ± 11.1	36.4 ± 10.5
Median (min, max)	35 (18, 60)	36 (19, 59)	36 (19, 61)	34 (18, 59)	35 (18, 60)	35 (18, 61)
Sex, n (%)						
Male	101 (66.9)	93 (64.1)	107 (73.3)	103 (70.1)	98 (70.0)	502 (68.9)
Female	50 (33.1)	52 (35.9)	39 (26.7)	44 (29.9)	42 (30.0)	227 (31.1)
Race, n (%)						
Caucasian	80 (53.0)	77 (53.1)	71 (48.6)	75 (51.0)	67 (47.9)	370 (50.8)
Non-Caucasian	71 (47.0)	68 (46.9)	75 (51.4)	72 (49.0)	73 (52.1)	359 (49.2)
Black/African American	34 (22.5)	32 (22.1)	38 (26.0)	32 (21.8)	35 (25.0)	171 (23.5)
Asian	36 (23.8)	34 (23.4)	37 (25.3)	39 (26.5)	37 (26.4)	183 (25.1)
American Indian/Alaska native	1 (0.7)	2 (1.4)	0	0	0	3 (0.4)
Other	0	0	0	1 (0.7)	1 (0.7)	2 (0.3)
Ethnicity, n (%)						
Hispanic or Latino	6 (4.0)	7 (4.8)	2 (1.4)	4 (2.7)	5 (3.6)	24 (3.3)
Not Hispanic or Latino	145 (96.0)	138 (95.2)	144 (98.6)	143 (97.3)	135 (96.4)	705 (96.7)

Note: Percentages are relative to the Safety Population.

max = maximum; min = minimum; N = number of patients in the Safety Population; n = number of patients in the specified category.

Characteristic	*Placebo (N = 151)*	*Cariprazine, mg/day*			*Risperidone 4.0 mg/day (N = 140)*
		1.5 (N = 145)	*3.0 (N = 146)*	*4.5 (N = 147)*	
Schizophrenia subtype, n (%)					
Disorganized	9 (6.0)	5 (3.4)	7 (4.8)	4 (2.7)	8 (5.7)
Catatonic	0	0	0	1 (0.7)	1 (0.7)
Paranoid	130 (86.1)	131 (90.3)	132 (90.4)	134 (91.2)	121 (86.4)
Undifferentiated	12 (7.9)	9 (6.2)	7 (4.8)	8 (5.4)	10 (7.1)
Duration of schizophrenia, y					
Mean ± SD	11.6 ± 9.7	11.4 ± 8.7	11.2 ± 8.6	11.1 ± 9.8	12.3 ± 10.0
Median (min, max)	9 (1, 44)	10 (1, 33)	9 (1, 34)	7 (1, 43)	9 (1, 42)
Number of previous psychiatric hospitalizations					
Mean ± SD	5.6 ± 5.7	6.3 ± 8.4	5.6 ± 6.5	7.0 ± 8.6	6.3 ± 8.1
Median (min, max)	4 (0, 30)	4 (0, 60)	4 (0, 40)	4 (0, 50)	4 (0, 54)
Suicide and violence history, n (%)					
Attempted suicide	16 (10.6)	32 (22.1)	28 (19.2)	31 (21.1)	22 (15.7)
Violent	19 (12.6)	20 (13.8)	11 (7.5)	11 (7.5)	15 (10.7)

Note: Percentages are relative to the Safety Population.

There were no statistically significant differences among the treatment groups with respect to demographics and physical characteristics. In general, the distribution of concurrent medical conditions was similar across treatment groups.

Efficacy Parameter	Placebo (N = 148)	RGH-188 1.5 mg (N = 140)	RGH-188 3.0 mg (N = 140)	RGH-188 4.5 mg (N = 145)	Risperidone 4.0 mg (N = 138)	Total (N = 711)	P-value
PANSS Total Score							
Mean	97.3	97.1	97.2	96.7	98.1	97.3	0.752
SD	9.22	9.13	8.66	9.01	9.50	9.09	
Median	96.5	95.0	96.5	95.0	98.0	96.0	
Min, Max	80, 120	80, 119	80, 120	80, 120	80, 120	80, 120	
n	148	140	140	145	138	711	
PANSS Positive Subscale							
Mean	25.4	25.2	25.5	25.5	25.4	25.4	0.892
SD	3.85	3.69	3.89	3.98	3.70	3.81	
Median	26.0	25.0	25.0	26.0	25.0	25.0	
Min, Max	14, 35	17, 34	17, 36	16, 37	16, 36	14, 37	
n	148	140	140	145	138	711	
PANSS Negative Subscale							
Mean	25.2	24.3	24.5	24.5	25.2	24.7	0.161
SD	4.25	4.24	4.24	4.32	4.52	4.32	
Median	25.0	24.0	24.0	24.0	25.0	25.0	
Min, Max	11, 37	13, 37	12, 38	14, 36	15, 37	11, 38	
n	148	140	140	145	138	711	
CGI-S Score							
Mean	4.9	4.7	4.9	4.8	4.8	4.8	0.037
SD	0.62	0.55	0.60	0.58	0.69	0.61	
Median	5.0	5.0	5.0	5.0	5.0	5.0	
Min, Max	4, 6	4, 6	4, 7	4, 6	4, 6	4, 7	
n	148	140	140	145	138	711	

CGI-S Rating, n(%)							
Normal, not at all ill	0	0	0	0	0	0	0.016
Borderline ill	0	0	0	0	0	0	
Mildly ill	0	0	0	0	0	0	
Moderately ill	41 (27.7)	47 (33.6)	32 (22.9)	43 (29.7)	46 (34.8)	211 (29.7)	
Markedly ill	88 (59.5)	86 (61.4)	92 (65.7)	90 (62.1)	68 (49.3)	424 (59.6)	
Severely ill	19 (12.8)	7 (5.0)	15 (10.7)	12 (8.3)	22 (15.9)	75 (10.5)	
Among the most extremely ill patients	0	0	1 (0.7)	0	0	1 (0.1)	
NSA-16 Total Score							
Mean	55.8	55.1	55.9	54.9	55.5	55.4	0.844
SD	10.66	12.07	11.80	11.09	12.61	11.62	
Median	55.0	57.0	56.0	55.0	55.5	56.0	
Min, Max	28, 87	26, 87	22, 87	29, 85	24, 87	22, 87	
n	148	140	140	145	138	711	
NSA Global Negative Symptom Rating							
Mean	4.1	4.1	4.0	4.0	4.1	4.1	0.857
SD	0.84	0.88	0.79	0.91	1.02	0.89	
Median	4.0	4.0	4.0	4.0	4.0	4.0	
Min, Max	2, 6	2, 6	2, 6	2, 6	1, 6	1, 6	
n	148	140	140	145	138	711	

The treatment groups were generally well-balanced on the PANSS but a significant difference was observed in the CGI-S score. The baseline score was a covariate in the ANCOVA models used in the analysis of the efficacy parameters, this imbalance did not confound the results.

Similar proportions of patients in each treatment group used at least one medication during the double-blind treatment period. Psycholeptics, anti-parkinsonian drugs, analgesics, and anti-inflammatory/anti-rheumatic agent were the most commonly used drugs classes. Anti-parkinsonian drugs, which were to be administered only after EPS scales were performed in order to support their administration, tended to be used by fewer patients in the placebo (17.2%) and the cariprazine 1.5 mg/day (19.3%) groups relative to cariprazine 4.5 mg/day (24.5%) and risperidone (28.6%) treatment groups. Rescue medication was used equally in the treatment groups.

Numbers analysed

A total of 732 patients were randomised and approximately two thirds (63.6%) completed the study. The most frequent reasons for discontinuation were insufficient response (12.8%), withdrawal of consent (11.7%) and AEs (9.5%). A statistically significantly greater percentage of patients in the placebo group discontinued because of insufficient therapeutic response compared to the cariprazine groups and the risperidone group. Fewer patients in the cariprazine and risperidone treatment groups compared with the placebo group discontinued because of adverse events.

Outcomes and estimation

Primary endpoint

The primary efficacy parameter was the change from baseline to week 6 in the PANSS total score using the LOCF approach. Statistical significance over placebo was observed for the average of the 3.0 and 4.5 mg/day cariprazine treatments groups as well as for each cariprazine treatment group (1.5, 3.0 and 4.5 mg/day) and for the risperidone treatment group. The mean change in the PANSS total score using the MMRM analysis was statistically significant relative to placebo for the average of the 3.0 and 4.5 mg/day cariprazine treatment groups and as well as for each of the cariprazine treatment groups. However, for the OC analyses, the average effect of the cariprazine treatment groups was not statistically significant relative to placebo. For the risperidone treatment group, the mean change in the PANSS total score at week 6 relative to placebo was statistically significant for both the MMRM and OC analyses.

Table 12. Change from baseline to week 6 in the PANSS-T score (LOCF)-ITT population:

	Placebo (N = 148)	*Cariprazine, mg/day*			*Risperidone 4.0 mg/day N = 138)*	*p-Value[a]*
		1.5 (N = 140)	*3.0 (N = 140)*	*4.5 (N = 145)*		
Baseline, mean ± SEM	97.3 ± 0.8	97.1 ± 0.8	97.2 ± 0.7	96.7 ± 0.8	98.1 ± 0.8	
Change at Week 6, mean ± SEM	–9.5 ± 1.6	–17.3 ± 1.7	–18.7 ± 1.8	–20.2 ± 1.6	–25.3 ± 1.7	< 0.0001
LSMD (95% CI)[b]	—	–7.5 (–11.8, –3.3)	–8.8 (–13.1, –4.6)	–10.4 (–14.6, –6.2)	–15.0 (–19.4, –10.8)	
p-Value[b]	—	0.0005	< 0.0001	< 0.0001	< 0.0001	

Note: p-Values were based on an ANCOVA model for change from baseline, with treatment group and pooled study center as factors and the baseline value as a covariate.

a p-Value for the comparison of the average effect of cariprazine 3.0 mg/day and cariprazine 4.5 mg/day with that of placebo.

b Comparison of the corresponding treatment group to placebo.

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LSMD = least squares mean difference; PANSS = Positive and Negative Syndrome Scale.

Table 13. Change from baseline to week 6 in the PANSS-T score (OC and MMRM)-ITT population

	Placebo (N = 148)	*Cariprazine, mg/day*			*Risperidone 4.0 mg/day (N = 138)*	*p-Value[a]*
		1.5 (N = 140)	*3.0 (N = 140)*	*4.5 (N = 145)*		
Change at Week 6, OC						
n	79	90	97	100	101	0.1598
Baseline, mean ± SEM	96.6 ± 1.1	97.4 ± 1.0	96.7 ± 0.9	96.9 ± 0.9	98.0 ± 0.9	
Change, mean ± SEM	–21.9 ± 1.8	–26.7 ± 1.8	–25.4 ± 2.0	–27.9 ± 1.5	–32.2 ± 1.7	
LSMD (95% CI)[b]	—	–3.0 (–7.2, 1.2)	–1.4 (–5.5, 2.7)	–3.8 (–7.9, 0.3)	–7.4 (–11.6, –3.3)	
p-Value[b]	—	0.1564	0.5067	0.0691	0.0004	
Change at Week 6, MMRM						
LS mean ± SE	–13.3 ± 1.8	–21.3 ± 1.8	–21.5 ± 1.7	–23.8 ± 1.7	–29.3 (1.7)	< 0.0001
LSMD (95% CI)[b]	—	–8.0 (–12.9, –3.0)	–8.2 (–13.1, –3.2)	–10.5 (–15.4, –5.6)	–16.0 (–20.9, –11.4)	
p-Value[b]	—	0.0017	0.0013	< 0.0001	< 0.0001	

Note: p-Values for the OC analysis were based on an ANCOVA model for change from baseline, with treatment group and pooled study center as factors and the baseline value as a covariate. p-Values for the MMRM analysis were based on a mixed model for repeated measurements with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, the baseline value and baseline-by-visit interaction as covariates, and an unstructured covariance matrix.

a p-Value for the comparison of the average effect of cariprazine 3.0 mg/day and cariprazine 4.5 mg/day with that of placebo.

b Comparison of the corresponding treatment group to placebo.

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; n = number of patients included in the analysis; N = number of patients in the Intent-to-Treat Population; PANSS = Positive and Negative Syndrome Scale.

The secondary efficacy endpoint

The secondary efficacy endpoint was the change from baseline to week 6 in the CGI-S score using the LOCF approach. The change from baseline to week 6 in the CGI-S score averaged for the 3.0 and 4.5 mg/day cariprazine treatment groups as well as for each cariprazine treatment group. The MMRM analysis also showed statistical significance relative to placebo for the average effect of the cariprazine 3.0 and 4.5 mg/day treatment groups and for each cariprazine treatment group. However, for the OC analyses, the average effect of the cariprazine treatment groups was not statistically significant relative to placebo. For the risperidone treatment group, the change in the CGI-S score at week 6 relative to placebo was statistically significant using the LOCF and OC approach and the MMRM analysis.

Table 14. Change from baseline to week 6 in the CGI-S score-ITT population:

	Placebo (N = 148)	*Cariprazine, mg/day*			*Risperidone 4.0 mg/day (N = 138)*	*p-Value[a]*
		1.5 (N = 140)	*3.0 (N = 140)*	*4.5 (N = 145)*		
Change at Week 6, LOCF						
n	148	140	140	145	138	
Baseline, mean ± SEM	4.9 ± 0.1	4.7 ± 0.1	4.9 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	
Change, mean ± SEM	–0.6 ± 0.1	–0.9 ± 0.1	–1.1 ± 0.1	–1.2 ± 0.1	–1.4 ± 0.1	<0.0001[b]
LSMD (95% CI)[c]	—	–0.4 (–0.6, –0.1)	–0.5 (–0.7, –0.2)	–0.6 (–0.9, –0.4)	–0.8 (–1.1, –0.6)	
p-Value[c]	—	0.0040	0.0003	< 0.0001	< 0.0001	

Table 15. Change from baseline to week 6 in the CGI-S score-ITT population

	Placebo (N = 148)	*Cariprazine, mg/day*			*Risperidone 4.0 mg/day (N = 138)*	*p-Value[a]*
		1.5 (N = 140)	*3.0 (N = 140)*	*4.5 (N = 145)*		
Change at Week 6, OC						
n	79	90	97	100	102	0.2244
Baseline ± SEM	4.8 ± 0.1	4.7 ± 0.1	4.9 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	
Change, mean ± SEM	–1.3 ± 0.1	–1.3 ± 0.1	–1.4 ± 0.1	–1.6 ± 0.1	–1.8 ± 0.1	
LSMD (95% CI)[c]	—	–0.1 (–0.3, 0.2)	–0.0 (–0.2, 2.3)	–0.3 (–0.5, –0.0)	–0.3 (–0.6, –0.1)	
p-Value[c]	—	0.5476	0.9704	0.0353	0.0052	
Change at Week 6, MMRM						
LS mean ± SE	–0.9 ± 0.1	–1.2 ± 0.1	–1.2 ± 0.9	–1.5 ± 0.1	–1.6 ± 0 .1	0.0003
LSMD (95% CI)[c]	—	–0.3 (–0.6, –0.0)	–0.3 (–0.6, –0.0)	–0.6 (–0.8, –0.3)	–0.7 (–1.0, –0.4)	
p-Value[c]	—	0.0253	0.0243	< 0.0001	< 0.0001	

Note: p-Values for the LOCF and OC analyses were based on an ANCOVA model for change from baseline, with treatment group and pooled study center as fixed effects and the baseline value as a covariate. p-Values for the MMRM analysis were based on a mixed model for repeated measurements with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, the baseline value and baseline-by-visit interaction as covariates, and an unstructured covariance matrix.

a p-Value for the comparison of the average effect of cariprazine 3.0 mg/day and cariprazine 4.5 mg/day with that of placebo.

b p-Value was based on an analysis of variance model, with treatment group and study center (pooled) as factors.

c Comparison of the corresponding treatment group to placebo.

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; LOCF = last observation carried forward; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; n = number of patients included in the analysis; N = number of patients in the Intent-to-Treat Population; OC = observed cases; SEM = standard error of the mean.

Ancillary analyses

Additional efficacy parameters were the change form baseline to week 6 in the NSA-16 total score, the NSA-16 global negative symptom rating, PANSS positive score, the PANSS negative score, the CGI-I at week 6 and the percentage of PANSS responders at week 6. For all additional efficacy parameters, the average effect of the cariprazine 3.0 and 4.5 mg/day treatment groups and the 3 individual cariprazine treatment groups, as well as the risperidone treatment group showed significant improvement relative to placebo.

RGH-MD-06

A randomized, double-blind, placebo –controlled, parallel-group study of cariprazine (RGH-188) in the prevention of relapse in patients with schizophrenia

Methods

This was a multinational, multicentre, randomized, double-blind, placebo-controlled, parallel-group, study, in the prevention of relapse in patients with schizophrenia. This study was carried out in 5 phases.

The screening phase was a no-drug washout phase of up to seven days during which the patient eligibility was assessed, followed by the run-in phase (RIP) during which patients received open-label cariprazine, flexibly dosed for the first 6 weeks and for the last 2 weeks the dose was fixed. Patients continued to the stabilization phase (SP) only if they met the predefined criteria: completion of the 8-week RIP, PANSS total score ≤ 60 at visit 8, at least 20% decrease in PANSS total score from baseline to end of week 8, CGI-S score ≤ 4 at visit 8, score of ≤4 on each of the following 7 PANSS items: P1, P2, P3, P6, P7, G8, and G14 at visit 8, stable dose during the last 2 weeks of the RIP, no significant tolerability issues as judged by the investigator at visit 8. During the SP, patients received 12 weeks of open-label treatment with cariprazine (3, 6, or 9 mg/day), the same dose that they were receiving in the last 2 weeks of the RIP. At visit 14, the double-blind phase (DBP) started and the patients were randomized to 1 of 2 treatment groups (cariprazine or placebo) in a 1:1 ration only if they met all of the following criteria: completion of the 12-week SP, PANSS total score ≤ 60 at visit 14, at least 20% decrease in PANSS total score from baseline to end of week 20, CGI-S score ≤ 4 at visit 14, score of ≤4 on each of the following 7 PANSS items: P1, P2, P3, P6, P7, G8, and G14 at visit 14, no significant tolerability issues as judged by the investigator at visit 14. During the DBP patients received either placebo or cariprazine at the same dose that they received during the SP. The duration of the DBP was variable (a maximum of 72 week and a minimum of 26 weeks or until ET including a relapse event). All patients were hospitalized during the screening phase and for the first 2 weeks of the RIP. They may remain hospitalized for an additional 2 weeks. Patients who completed the study or who prematurely discontinued were followed for 4 more weeks, safety follow-up phase (SFU). During the SFU phase the patients received treatment as usual.

Study Participants

Male or female inpatients 18-60 years of age, with a DSM-IV diagnosis of schizophrenia (disorganized, catatonic, paranoid, or undifferentiated) as determined by Structured Clinical Interview for DSM-IV (SCID) for a minimum of 1 year. Patients were required to have a PANSS-T score ≥70 and ≤120 at visit 1 and visit 2. Patients were also required to have a rating of at least 4 (moderate) on at least 2 of the following 4 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness/persecution

Treatments

The cariprazine dosage ranged from 3 to 9 mg/day administered as a single dose in the evening. After the no-drug screening phase, all patients still meeting the eligibility criteria, continued to the RIP and were administered cariprazine 1.5 mg on day 1 and 3.0 mg on day 2. On day 4 the dose could be increased to 4.5 mg/day, on day 6 to 6.0 mg/day and to 9 mg/day on day 10. The dose was only increased if response was not adequate and no tolerability problems were found. For the last 2 weeks the dose was fixed.

Objectives

The objective of this study was to evaluate the efficacy and safety of cariprazine (RGH-188) relative to placebo in the prevention of relapse of symptoms in patients with schizophrenia.

Outcomes/endpoints

The primary efficacy parameter was time to first relapse during the DBP.

Relapse was defined as meeting any of the following criteria:

- Psychiatric hospitalization due to worsening of the patient´s underlying condition
- Increase in PANSS total score by ≥30% for patients who scored 50 or higher at randomization or a 10-point or more increase for patients who scored less than 50 at randomization.
- Increase in the visit 14 CGI-S score by 2 or more points.
- Deliberate self-injury or aggressive/violent behaviour.
- Suicidal or homicidal ideation that was clinically significant.
- Score of > 4 on 1 or more of the following PANSS items: P1, P2, P3, P, P7, G8, or G14.

The additional efficacy variables

- Change from baseline in PANSS total score
- Change from baseline in PANSS positive and PANSS negative score
- Change from baseline in PSP scale score
- Change from baseline in CGI-S score
- CGI-I score
- Change from baseline in NSA-16 total score

Sample size

The calculation of power was based on a relapse hazard ratio of 0.48. This assumed a cumulative relapse rate at 26 weeks of 25% for the cariprazine group versus 45% for the placebo group. Under the assumption of constant hazard rates, this was equivalent to median times to relapse of 63 weeks for the cariprazine group versus 30 weeks for the placebo group. In addition, the calculation of power assumed a cumulative ET rate of 20% at 26 weeks due to reasons other than relapse for both treatment groups.

Using these assumptions, a total of ≈80 relapse events in the DBP needed be observed in order to have 90% power to detect a statistically significant difference between cariprazine and placebo, using 2-tailed, log-rank tests at an overall 5% level of significance. A total of ≈180 patients (≈90 patients per treatment group), randomized into the DBP at an average rate of approximately 4 patients per week, would have provided, on average, the required total of 80 relapse events in the DBP.

Randomisation and blinding

At visit 14 the patients were randomized to 1 of 2 treatment groups (cariprazine or placebo) in a 1:1 ratio.

Statistical methods

The Open-label Intent-to-Treat (ITT) Population consisted of all patients in the Run-in Phase Safety Population who had at least 1 post baseline assessment of the PANSS during the open-label phase (OLP) of the study.

The Randomized Population consisted of all patients in the Stabilization Phase Safety Population who were randomized to a treatment group during the DBP of the study.

The Double-blind ITT Population consisted of all patients in the Double-blind Safety Population who had at least 1 post randomization assessment of PANSS or CGI-S during the DBP of the study.

The primary efficacy parameter was the time to first relapse during the DBP, defined as the number of days from the randomization date to the relapse date. Relapse during the DBP was defined as meeting 1

or more of the following criteria: 1. Psychiatric hospitalization due to worsening of the patient's underlying condition; 2. Increase in PANSS total score by ≥ 30% for patients who scored 50 or higher at randomization or a 10-point or more increase for patients who scored less than 50 at randomization; 3. Increase in the Visit 14 CGI-S score by 2 or more points 4. Deliberate self-injury or aggressive/violent behavior; 5. Suicidal or homicidal ideation that was clinically significant as judged by the Investigator; 6. Score of greater than 4 on 1 or more of the following PANSS items: P1, P2, P3, P6, P7, G8 or G14. Criteria 2, 3, and 6 were to be confirmed at a repeat visit within 7 days, unless the repeat visit did not occur based on the discretion of the Investigator and noted in the eCRF.

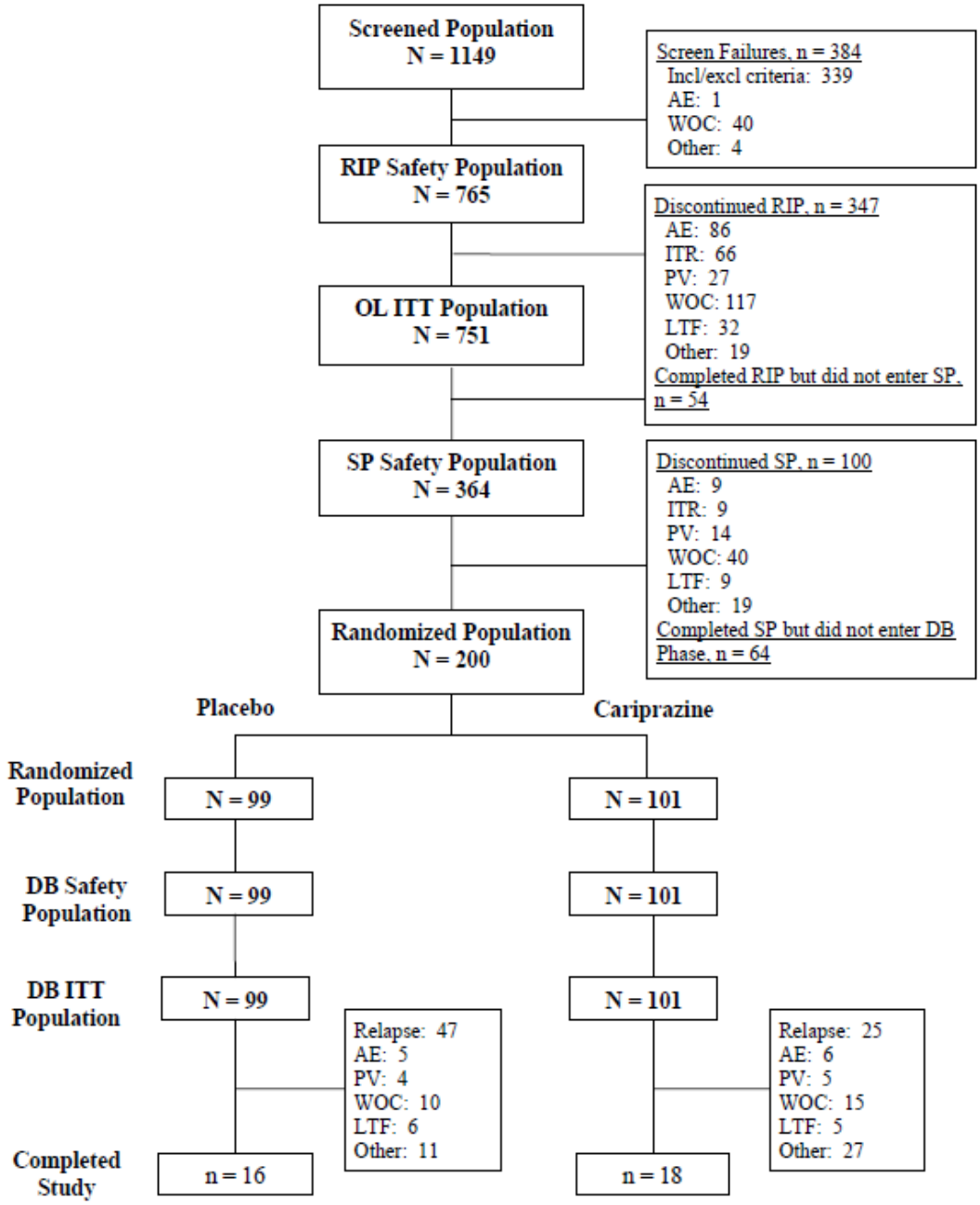
Patients who did not meet the above relapse criteria were censored at the time of completion or discontinuation from the study.

The primary efficacy analysis compared the time to relapse between placebo and cariprazine groups using the log-rank test. Estimates of the hazard ratio and 95% confidence intervals were based on the Cox proportional hazards model with treatment group as explanatory variable. The cumulative distribution function of time to relapse was characterized by the Kaplan-Meier estimate and curves.

A post hoc sensitivity analysis was performed using reference-based controlled imputation to assess the robustness of the primary analysis results to the potential violation of the noninformative censoring assumption. The referenced-based sensitivity analysis uses a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analysis toward the informative censoring, which assumes that the hazard of relapse for cariprazine-treated patients who discontinued is the same as the hazard for relapse for placebo-treated patients. A multiple imputation approach was used to implement the reference-based sensitivity analysis. Two hundred imputations were used to enhance the stability of the estimates.

Results

Participant flow



AE = adverse event; DB = double-blind; incl/excl = inclusion or exclusion; ITR = insufficient therapeutic response; ITT = intent-to-treat; LTF = lost to follow-up; N = number of patients in the specified population; n = number of patients in the specified category; OL = open-label; PV = protocol violation; RIP = run-in phase; stabilization phase; WOC = withdrawal of consent.

Recruitment

The first patient was enrolled 27 September 2011 and the last patient completed the last visit 03 September 2014.

Conduct of the study

This was a multi-centre study with 72 centres in total; 25 in the US, 15 in India, 10 in Romania, 7 in Slovakia, and 15 in Ukraine.

Baseline data

Table 16. Demographic characteristics at run-in phase safety population and double-blind safety population:

	Run-in Phase Safety Population	*Double-blind Safety Population*		
Characteristic	*Cariprazine 3-9 mg (N = 765)*	*Placebo (N = 99)*	*Cariprazine 3-9 mg (N = 101)*	*Total (N = 200)*
Age, years				
Mean ± SD	38.4 ± 10.4	37.7 ± 10.1	39.2 ± 10.9	38.4 ± 10.5
Min, max	18, 60	21, 58	18, 60	18, 60
Sex, n (%)				
Male	544 (71.1)	70 (70.7)	62 (61.4)[a]	132 (66.0)
Female	221 (28.9)	29 (29.3)	39 (38.6)	68 (34.0)
Race, n (%)				
White	299 (39.1)	38 (38.4)	45 (44.6)	83 (41.5)
All other races	466 (60.9)	61 (61.6)	56 (55.4)	117 (58.5)
Black	313 (40.9)	30 (30.3)	31 (30.7)	61 (30.5)
Asian	149 (19.5)	30 (30.3)	25 (24.8)	55 (27.5)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0	0	0
Other	3 (0.4)	1 (1.0)	0	1 (0.5)
Ethnicity, n (%)				
Hispanic or Latino	37 (4.8)	4 (4.0)	5 (5.0)	9 (4.5)
Not Hispanic or Latino	728 (95.2)	95 (96.0)	96 (95.0)	191 (95.5)
Weight, kg				
Mean ± SD	78.07 ± 20.10	74.94 ± 18.45	75.84 ± 20.34	75.39 ± 19.39
Min, max	35.0, 143.2	35.0, 122.1	38.4, 137.0	35.0, 137.0
Height, cm				
Mean ± SD	170.98 ± 9.95	168.62 ± 9.06	168.85 ± 10.99	168.74 ± 10.05
Min, max	138.0, 196.0	138.0, 190.5	140.0, 193.0	138.0, 193.0
BMI, kg/m^2				
Mean ± SD	26.50 ± 5.63	26.21 ± 5.53	26.39 ± 5.87	26.30 ± 5.69
Min, max	18.0, 41.0	18.2, 40.0	18.1, 39.0	18.1, 40.0
Waist Circumference, cm				
Mean ± SD	90.39 ± 15.34	89.19 ± 14.89	89.95 ± 16.42	89.57 ± 15.65
Min, max	48.5, 142.0	48.5, 137.0	55.4, 127.0	48.5, 137.0

a Statistically significant difference between treatment groups in the ratio of males and females based on the Cochran-Mantel-Haenszel test controlling for study center (p = 0.0361).

Table 17. Psychiatric history- run-in phase safety population and double-blind safety population

	Run-in Phase Safety Population	*Double-blind Safety Population*		
	Cariprazine 3-9 mg (N = 765)	*Placebo (N = 99)*	*Cariprazine 3-9 mg (N = 101)*	*Total (N = 200)*
Schizophrenia, n (%)				
Disorganized	7 (0.9)	1 (1.0)	0	1 (0.5)
Paranoid	712 (93.1)	94 (94.9)	97 (96.0)	191 (95.5)
Undifferentiated	46 (6.0)	4 (4.0)	4 (4.0)	8 (4.0)
Age at onset of original diagnosis, years				
Mean ± SD	25.5 ± 8.7	27.2 ± 8.6	27.2 ± 9.2	27.2 ± 8.9
Min, max	5, 56	5, 48	9, 54	5, 54
Duration of schizophrenia, years				
Mean ± SD	12.89 ± 10.17	10.49 ± 9.54	11.94 ± 10.36	11.22 ± 9.96
Min, max	1.0, 47.0	1.1, 47.0	1.1, 44.3	1.1, 47.0
Age at onset of current episode, years				
Mean ± SD	38.3 ± 10.4	37.7 ± 10.1	39.1 ± 10.9	38.4 ± 10.5
Min, max	18, 60	21, 58	18, 60	18, 60
Duration of current episode, weeks				
Mean ± SD	2.15 ± 0.92	2.16 ± 1.02	2.09 ± 0.93	2.12 ± 0.97
Min, max	0.1, 7.0	0.3, 7.0	0.1, 5.9	0.1, 7.0
Number of previous psychiatric hospitalizations				
Mean ± SD	6.4 ± 8.8	3.8 ± 4.4	5.3 ± 6.1	4.6 ± 5.4
Min, max	0, 99	0, 20	0, 30	0, 30
Number of exacerbations of schizophrenia during the last year				
Mean ± SD	1.5 ± 1.1	1.4 ± 1.0	1.5 ± 0.9	1.4 ± 1.0
Min, max	0, 12	0, 5	0, 6	0, 6
Attempted suicide?				
Yes, n (%)	123 (16.1)	14 (14.1)	12 (11.9)	26 (13.0)
Violent?				
Yes, n (%)	70 (9.2)	7 (7.1)	10 (9.9)	17 (8.5)

Table 18. Baseline-efficacy variables-open label ITT population and double-blind ITT population

Efficacy Parameter	*Open-label ITT Population*	*Double-blind ITT Population*		
	Cariprazine 3-9 mg (N = 751)	*Placebo (N = 99)*	*Cariprazine 3-9 mg (N = 101)*	*Total (N = 200)*
PANSS total score, mean ± SD	91.3 ± 10.1	50.5 ± 6.1	51.3 ± 7.2	50.9 ± 6.7
PANSS positive subscale score, mean ± SD	24.4 ± 3.7	11.5 ± 2.4	11.8 ± 2.9	11.6 ± 2.6
PANSS negative subscale score, mean ± SD	22.8 ± 4.3	14.3 ± 3.1	14.2 ± 3.4	14.3 ± 3.3
NSA-16 total score, mean ± SD	52.4 ± 11.7	38.0 ± 9.3	39.2 ± 10.0	38.6 ± 9.7
PSP total score, mean ± SD	48.5 ± 10.1	68.5 ± 9.0	66.5 ± 9.5	67.5 ± 9.3
CGI-S score, mean ± SD	4.7 ± 0.6	2.6 ± 0.6[a]	2.8 ± 0.6[a]	2.7 ± 0.6
Distribution of CGI-S scores at baseline, n (%)				
Normal, not at all ill	0	4 (4.0)	2 (2.0)	6 (3.0)
Borderline ill	0	31 (31.3)	22 (21.8)	53 (26.5)
Mildly ill	1 (0.1)	61 (61.6)	70 (69.3)	131 (65.5)
Moderately ill	286 (38.1)	3 (3.0)	7 (6.9)	10 (5.0)
Markedly ill	408 (54.3)	0	0	0
Severely ill	56 (7.5)	0	0	0
Among the most extremely ill patients	0	0	0	0

Note: Baseline for the open-label phase is defined as the last assessment prior to the first dose of open-label investigational product. Baseline for the double-blind phase is defined as the last assessment at or prior to the first dose of double-blind investigational product at Visit 14 (Week 20).

a A statistically significant difference was observed between the placebo and cariprazine treatment groups in the Double-blind ITT Population for CGI-S score, based on a 2-way ANOVA with treatment group and study center as factors (p = 0.0183).

ANOVA = analysis of variance; CGI-S = Clinical Global Impressions–Severity; ITT = intent-to-treat; NSA-16 = 16-Item Negative Symptom Assessment scale; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance scale.

Numbers analysed

Of the 1149 patients who were screened for eligibility, 765 patients were enrolled and entered the RIP and 364 patients continued into the SP. A total of 200 patients who completed the open-label treatment phase of the study were randomised to either placebo or cariprazine. The most frequent reasons for discontinuation during the OLP were withdrawal of consent and AEs. Discontinuation due to AEs occurred more frequently in the RIP than in the SP.

Outcomes and estimation

The time to first relapse during the DBP was the primary efficacy parameter. By the end of the DBP, 47.5% of placebo-treated patients and 24.8% of cariprazine-treated patients had a relapse of schizophrenia. Time to relapse was significantly longer in the cariprazine group.

Table 19. Primary efficacy analysis: survival analysis summary of time to first relapse during the double-blind treatment period-double blind intent to treat population

	Placebo (N = 99)	*Cariprazine 3-9 mg (N = 101)*
Number censored	52	76
Number of events	47	25
Crude rate of event, %	47.5	24.8
Time to relapse, days[a]		
25% percentile (95% CI)	92 (44, 151)	224 (99, -)
50% percentile (95% CI)	296 (157, -)	—
75% percentile (95% CI)	—	—
P-value[b]	—	0.0010
Hazard ratio[c] (95% CI)	—	0.45 (0.28, 0.73)

Note: Time to first relapse (days) is calculated as the date of the first relapse – the date of randomization + 1. Patients who did not meet relapse criteria are considered censored at the time of completion or discontinuation from the double-blind phase of the study.

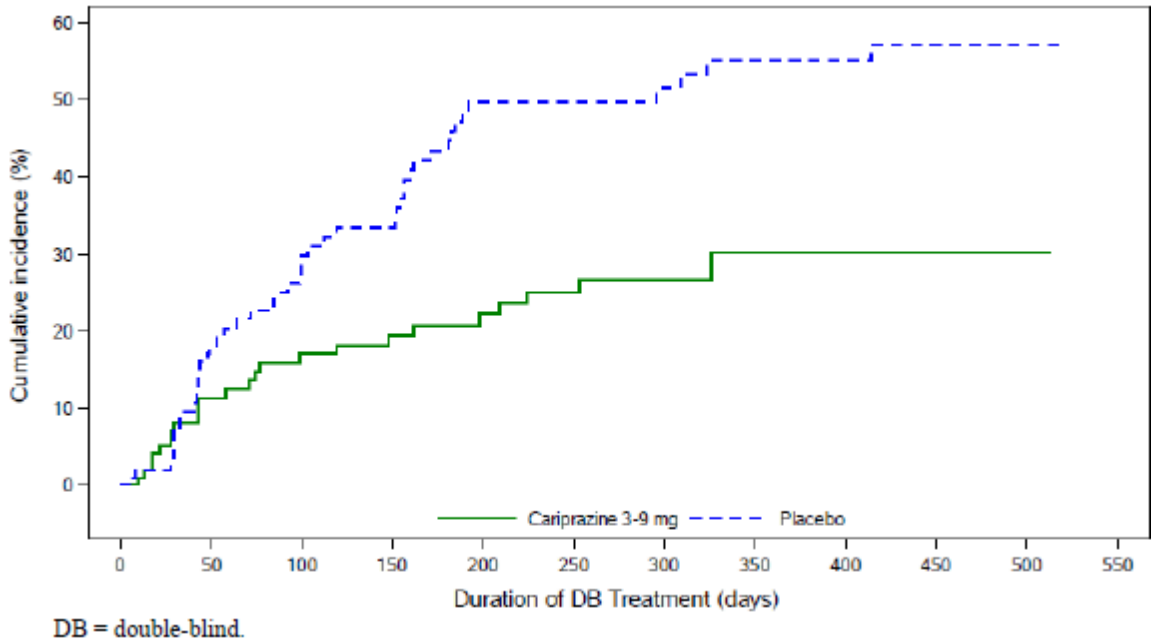
a Percentiles (95% CI) are based on Kaplan-Meier estimates.

b P-value is based on the log-rank test.

c Hazard ratio (cariprazine 3-9 mg vs placebo) is based on Cox proportional hazards regression model, with treatment group as an explanatory variable.

CI = confidence interval.

Kaplan-Meier curves of the cumulative rate of relapse:



DB = double-blind.

Table 20. Number of patients with relapse during the double-blind treatment period-double-blind intent-to-treat population

Relapse Category	*Placebo (N = 99) n (%)*	*Cariprazine 3-9 mg (N = 101) n (%)*
Patients who met any relapse criteria	**47 (47.5)**	**25 (24.8)**
Psychiatric hospitalization due to worsening of the patient's underlying condition	9 (9.1)	9 (8.9)
Increase in PANSS total score by ≥ 30% for patients who scored ≥ 50 at randomization or a ≥ 10-point increase for patients who scored < 50 at randomization	43 (43.4)	21 (20.8)
Increase in Visit 14 CGI-S score by ≥ 2 points	28 (28.3)	4 (4.0)
Deliberate self-injury or aggressive/violent behavior	4 (4.0)	0
Suicidal or homicidal ideation that was clinically significant as judged by the Investigator	0	0
Score of > 4 on 1 or more of the following PANSS items: P1, P2, P3, P6, P7, G8 or G14	25 (25.3)	11 (10.9)

Note: patients may have met more than 1 relapse criterion.
CGI-S = Clinical Global Impressions–Severity; PANSS = Positive and Negative Syndrome Scale.

Ancillary analyses

Additional efficacy parameters were the change from baseline in PANSS total scores and in positive and negative subscale scores. At the end of the open-label treatment with cariprazine, improvement from baseline scores was observed for the PANSS total score as well as for the positive and negative subscales. At the end of double-blind treatment, changes in scores form double-blind baseline were larger in the placebo group than in the cariprazine group for all PANSS scores. The changes in PANSS total score were similar for both the groups for the first 3-4 weeks of double-blind treatment and thereafter the change was greater in the placebo group.

Table 21. Change in PANSS scores at the end of the open-label phase and at the end of the double-blind treatment period-open-label ITT population and double-blind ITT population

	Open-label Phase	*Double-blind Treatment Period*	
	Cariprazine 3-9 mg (N = 751) Mean ± SD	*Placebo (N = 99) Mean ± SD*	*Cariprazine 3-9 mg (N = 101) Mean ± SD*
PANSS Total Score			
Baseline	91.3 ± 10.1	50.5 ± 6.1	51.3 ± 7.2
Postbaseline	68.5 ± 19.3	63.7 ± 19.1	56.2 ± 15.5
Change from baseline	–22.8 ± 19.8	13.2 ± 18.8	5.0 ± 14.2
PANSS Positive Subscale Score			
Baseline	24.4 ± 3.7	11.5 ± 2.4	11.8 ± 2.9
Postbaseline	17.0 ± 6.5	15.8 ± 6.2	13.1 ± 5.6
Change from baseline	–7.4 ± 6.5	4.3 ± 6.3	1.3 ± 5.5
PANSS Negative Subscale Score			
Baseline	22.8 ± 4.3	14.3 ± 3.1	14.2 ± 3.4
Postbaseline	17.9 ± 5.1	16.7 ± 5.1	15.6 ± 4.0
Change from baseline	–4.9 ± 5.3	2.4 ± 4.3	1.4 ± 3.5

Note: Baseline for the open-label phase is the last measurement before the start of open-label treatment.
Baseline for the double-blind treatment period is the last measurement during open-label treatment period.
ITT = intent-to treat; PANSS = Positive and Negative Syndrome Scale.

At the end of the open-label treatment, 46.7% of patients in the treatment group and at the end of double-blind treatment period 3% of patients in both the placebo and the cariprazine treated group had ≥30% improvement from baseline in PANSS total score.

Mean CGI-I score at the end of open-label treatment was 2.8 and at the end of double-blind treatment 3.1 in the placebo group and 2.5 in the cariprazine group.

Mean change from baseline in NSA-16 total score at the end of open-label treatment was -8.2 and at the end of double-blind treatment 4.1 in the placebo group and 0.6 in the cariprazine group.

Mean change form baseline in PSP scale score at the end of open-label treatment was 11.1 and at the end of double-blind treatment -7.2 in the placebo group and 0.0 in the cariprazine group.

RGH-188-005

A randomized, double-blind, parallel-group study to investigate the efficacy, safety, and tolerability of cariprazine in patients with predominant negative symptoms of schizophrenia

Methods

This was a multinational, multicentre, randomized, double-blind, active-referenced, parallel-group, fixed/flexible-dose, efficacy, and safety study, in adult patients with a primary diagnosis of schizophrenia having persistent, predominant negative symptoms and with a low level of positive symptoms. This study consisted of 3 periods. A 4-week prospective lead-in period was followed by a 26-week double-blind study treatment period, consisting of a 2-week study treatment up-titration phase and a 24-week study treatment continuation phase, and a 2-week safety follow-up period. At the screening visit, potential

patients were screened for the presence and the severity of negative symptoms. After the screening assessments, eligible patients entered the 4-week lead-in period during which the antipsychotic treatment was kept unchanged. An intermediate lead-in visit took place 14 days after the screening visit to assess the clinical status of the patients and they were reassessed using inclusion and exclusion criteria addressing stability. At the baseline visit the presence and the severity of the patient´s negative symptom and stability were again assessed. If the patients still were eligible for the study, they were randomized (1:1) to double-blind study medication, either cariprazine or risperidone. The 26-week double-blind study treatment period started thereafter.

Study Participants

Male or female patients 18-65 years of age, with a DSM-IV diagnosis of schizophrenia (i.e. 295), all subtypes allowed, as determined by Structured Clinical Interview for DSM-IV (SCID) for a minimum of 2 years. Predominant negative symptoms had to be present for at least 6 months at the screening visit. Patients were required to have a PANSS factor score for negative symptoms ≥24 and a score of ≥4 on a minimum 2 of the 3 PANSS items, N1-blunted affect, and N4-passive/apathetic social withdrawal, N6-lack of spontaneity and flow of conversation. A PANSS factor score for positive symptoms >19 was exclusionary. Patients were also excluded if rated a score of ≥4 on more than 2 of the following PANSS positive symptoms: delusions, hallucinatory behaviour, grandiosity, suspiciousness/persecution, and unusual thought content. A CDSS total score of >6 would also be exclusionary. At intermediate lead-in visit the patients would have to continue to meet the visit 1 eligibility criteria and have a PANSS factor score for negative symptoms that diverged from the screening score by <25%. A PANSS factor score for positive symptom increased from the screening score by 25% would be exclusionary. Patients were also excluded if required pharmacologic treatment for EPS. At baseline the above criteria were also used.

Treatments

The cariprazine target dose was 4.5 mg/day and dose range 3.0 to 6.0 mg/day administered as a single dose in the evening. For risperidone the target dose was 4-0 mg/day and dose range 3.0 to 6.0 mg/day. Eligible patients at the screening visit were untreated, treated with 1 or with a combination of 2 antipsychotic medications. After entering the study, the patients continued the same antipsychotic medication for the duration of the lead-in period. No changes were allowed during this period. The study treatment up-titration phase began on day 0 and from that day until day 6 patients received 1.5 mg/day of cariprazine or 2-0 mg/day of risperidone. From day 7 until day 13 the dose was increased to 3-0 mg of both cariprazine and risperidone. At the same time the dose of the antipsychotic medication that the patient took during the lead-in period was down titrated in 14 days. On day 14 the patients received the target dose of the study medication and the dose was fixed for 7 days. From day 21 until day 182 dose was in accordance with the dosing scheme and randomization schedule. The dose of the double-blind study medication could have been decreased/or increase in case of tolerability issues or impending psychotic deterioration, however only once during the study.

Objectives

The objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine for the treatment of patients with schizophrenia having predominant negative symptoms

Outcomes/endpoints

The primary efficacy parameter was the change from baseline to endpoint in the PANSS factor score for negative symptoms.

The secondary efficacy parameter was the change from baseline to endpoint in the personal and social performance scores.

Additional efficacy variables

- Change from baseline in CGI-S score at week 26
- Change from baseline in PANSS total score at week 26
- Change from baseline in PANSS positive, PANSS negative, and PANSS general psychopathology subscale scores at week 26
- CGI-I score at week 26
- Change from baseline in PSP self-care, socially useful activities, personal and social relationships, and disturbing and aggressive behaviour area scores at week 26
- Responders rates defined as a decrease of at least 20% in baseline PANSS factor score for negative symptoms at week 26

Pseudo specificity analyses

- Change from baseline in PANSS factor score for positive symptoms at week 26
- Change form baseline in CDSS total score at week 26

Sample size

The primary efficacy parameter was the change from baseline to Week 26 in the PANSS factor score for negative symptoms. A planned sample size of 210 patients per treatment group was expected to provide at least 90% power to detect an effect size (treatment group difference relative to pooled standard deviation) of 0.25 at a 2-sided significance level of 5%, assuming a treatment difference of 2.25 points and a pooled SD of 9 points, a correlation coefficient of 0.2 between repeated measurements and 10% attrition rate.

Randomisation and blinding

The patients were randomized (1:1) to double-blind study medication, either cariprazine or risperidone.

Statistical methods

For the LOCF approach, only the post baseline total score of a parameter was imputed; individual item scores were not carried forward. If the study IMP was stopped for more than 5 days prior to the final assessment, the penultimate assessment was carried forward instead. The baseline total score was carried forward only for the intermittent missing scores immediately after baseline. If all the post baseline values were missing, the baseline value was not carried forward.

The ITT population consisted of all patients in the safety population who had at least 1 post baseline assessment on the PANSS factor scores for negative symptoms.

The primary efficacy parameter of this study was the change from baseline to Endpoint (Week 26/ET) in the PANSS factor score for negative symptoms. The primary analysis was performed using an MMRM, with treatment group, study center, visit, and treatment group–by-visit interaction as fixed effects and the baseline value and baseline value–by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. However, in the event that this model did not converge, then the following covariance matrix would be used until the model converged: Toeplitz, first-order autoregressive and compound symmetry. Analysis was performed using PROC MIXED in SAS

and the resultant F-tests were based on Kenward-Roger's adjusted denominator degrees of freedom (Kenward 1997). This analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values.

A sensitivity analysis was performed using a pattern-mixture model, based on non-future dependent missing value restrictions (Kenward 2003) to assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption.

Analysis based on an analysis of covariance (ANCOVA) model using the LOCF approach was also performed. The ANCOVA model included treatment group and study center as factors and baseline PANSS factor score for negative symptoms as a covariate.

Results

Participant flow

Parameter	Cariprazine	Risperidone	Overall
Study Populations	N (%)	N (%)	N (%)
Screened [a]			533 (100)
Randomized [b]	230 (43.2)	231 (43.3)	461 (86.5)
Safety [c]	230 (43.2)	230 (43.2)	460 (86.3)
Intent to treat [d]	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) [e]	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)
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 [g]	52 (22.6)	52 (22.6)	104 (22.6)
During up-titration phase [h]	8 (3.5)	4 (1.7)	12 (2.6)
During treatment continuation phase [i]	44 (19.1)	48 (20.9)	92 (20.0)

Reasons for Early Termination in Decreasing Order by Frequency Overall (safety population) [j]	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 [k]	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)

Recruitment

Of the 533 patients who were screened, 461 patients were randomized and 460 patients were included in the safety population. A total of 356 patients (77.4%) completed the double-blind treatment period from baseline to week 26. The treatments were balanced with respect to the number and percentage of patients who discontinued early. The most common reasons for early discontinuation were AEs and withdrawal of consent. Discontinuation due to AEs occurred more frequently in the RIP than in the SP. Approximately 17% of patients in either treatment group completed the entire study.

Conduct of the study

This was a multi-centre study with 74 centres initiated and 66 of those screened or enrolled patients. The centres in the EU were located in Bulgaria, Croatia, Czech Republic, France, Hungary, Poland, Romania and Spain. In addition, Russia, Serbia and Ukraine recruited patients.

Baseline data

Table 22. Demographic characteristics, safety population

Parameter	Cariprazine N=230	Risperidone N=230	Overall N=460	P-Value Between Treatments [a]
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 [b]
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)	

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

a 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.

b Race was either white or not recorded (for France); p-values were not computed.

Table 23. 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 [a] 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 [a] 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
Duration of Last Psychiatric Hospitalization [a] (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

Abbreviations: N=number of patients overall; n (%)=number and percent of patients in the sample

a Data were included for any kind of psychiatric hospitalization, not only for an acute exacerbation.

Table 24. PANSS, PSP and CDSS scores at screening, intermediate lead-in visit and baseline visit, ITT population

Parameter	Visit	Statistic	Cariprazine (N = 227)	Risperidone (N = 229)	Overall (N = 456)
PANSS total score (range 30 to 210)	Screening	N	227	229	456
		Mean	77.6	77.4	77.5
		Median	77.0	76.0	77.0
		Std. Dev.	7.95	8.86	8.41
		Min, Max	61, 110	57, 110	57, 110
	Intermediate lead-in visit	N	227	229	456
		Mean	77.1	76.7	76.9
		Median	77.0	76.0	76.0
		Std. Dev.	7.97	8.38	8.17
		Min, Max	59, 109	57, 101	57, 109
	Baseline	N	227	229	456
		Mean	76.7	76.4	76.5
		Median	76.0	76.0	76.0
		Std. Dev.	8.07	8.16	8.11
		Min, Max	58, 109	57, 102	57, 109

Parameter	Visit	Statistic	Cariprazine (N = 227)	Risperidone (N = 229)	Overall (N = 456)
PANSS factor score for positive symptoms (range 5-35)	Screening	N	227	229	456
		Mean	9.0	9.0	9.0
		Median	9.0	9.0	9.0
		Std. Dev.	2.67	2.72	2.69
		Min, Max	5, 17	5, 16	5, 17
	Intermediate lead-in visit	N	227	229	456
		Mean	8.8	8.8	8.8
		Median	9.0	9.0	9.0
		Std. Dev.	2.70	2.61	2.66
		Min, Max	5, 16	5, 16	5, 16
	Baseline	N	227	229	456
		Mean	8.7	8.6	8.7
		Median	8.0	9.0	9.0
		Std. Dev.	2.72	2.64	2.68
		Min, Max	5, 16	5, 16	5, 16

Parameter	Visit	Statistic	Cariprazine (N = 227)	Risperidone (N = 229)	Overall (N = 456)
PANSS factor score for negative symptoms (range 7 to 49)	Screening	N	227	229	456
		Mean	27.8	27.6	27.7
		Median	28.0	27.0	27.0
		Std. Dev.	2.63	2.67	2.65
		Min, Max	24, 37	24, 38	24, 38
	Intermediate lead-in visit	N	227	229	456
		Mean	27.9	27.6	27.7
		Median	28.0	27.0	27.0
		Std. Dev.	2.56	2.50	2.53
		Min, Max	24, 36	24, 38	24, 38
	Baseline	N	227	229	456
		Mean	27.7	27.5	27.6
		Median	28.0	27.0	27.0
		Std. Dev.	2.57	2.39	2.48
		Min, Max	24, 36	24, 37	24, 37

Parameter	Visit	Statistic	Cariprazine (N = 227)	Risperidone (N = 229)	Overall (N = 456)
PANSS positive subscale score (range 7 to 49)	Screening	N	227	229	456
		Mean	12.3	12.3	12.3
		Median	12.0	12.0	12.0
		Std. Dev.	2.76	2.83	2.79
		Min, Max	7, 21	7, 20	7, 21
	Intermediate lead-in visit	N	227	229	456
		Mean	12.1	11.9	12.0
		Median	12.0	12.0	12.0
		Std. Dev.	2.91	2.69	2.80
		Min, Max	7, 21	7, 20	7, 21
	Baseline	N	227	229	456
		Mean	12.0	11.8	11.9
		Median	12.0	11.0	12.0
		Std. Dev.	2.78	2.72	2.75
		Min, Max	7, 21	7, 20	7, 21

Parameter	Visit	Statistic	Cariprazine (N = 227)	Risperidone (N = 229)	Overall (N = 456)
PANSS negative subscale score (range 7 to 49)	Screening	N	227	229	456
		Mean	28.5	28.2	28.4
		Median	29.0	28.0	28.0
		Std. Dev.	2.59	2.75	2.67
		Min, Max	22, 36	21, 37	21, 37
	Intermediate lead-in visit	N	227	229	456
		Mean	28.5	28.3	28.4
		Median	29.0	28.0	28.0
		Std. Dev.	2.47	2.70	2.59
		Min, Max	23, 36	21, 37	21, 37
	Baseline	N	227	229	456
		Mean	28.5	28.3	28.4
		Median	28.0	28.0	28.0
		Std. Dev.	2.52	2.67	2.60
		Min, Max	23, 36	21, 37	21, 37

Parameter	Visit	Statistic	Cariprazine (N = 227)	Risperidone (N = 229)	Overall (N = 456)
PANSS general psychopathology subscale score (range 16 to 112)	Screening	N	227	229	456
		Mean	36.9	36.9	36.9
		Median	37.0	37.0	37.0
		Std. Dev.	5.36	5.78	5.57
		Min, Max	23, 60	22, 56	22, 60
	Intermediate lead-in visit	N	227	229	456
		Mean	36.4	36.5	36.5
		Median	36.0	36.0	36.0
		Std. Dev.	5.45	5.58	5.51
		Min, Max	18, 60	22, 54	18, 60
	Baseline	N	227	229	456
		Mean	36.1	36.3	36.2
		Median	36.0	36.0	36.0
		Std. Dev.	5.47	5.54	5.50
		Min, Max	18, 60	19, 54	18, 60

Parameter	Visit	Value	Statistic	Cariprazine (N = 230)	Risperidone (N = 230)	Overall (N = 460)
Total PSP score (range 1 to 100)	Screening[1]		N	230	230	460
			Mean	48.6	47.5	48.1
			Median	50.0	50.0	50.0
			Std. Dev.	10.82	10.54	10.68
			Min, Max	23, 77	22, 75	22, 77
	Baseline		N	230	230	460
			Mean	48.8	48.1	48.4
			Median	50.0	49.0	50.0
			Std. Dev.	10.81	10.70	10.75
			Min, Max	21, 70	22, 75	21, 75

Calgary Depression Scale for Schizophrenia at Screening and Baseline Visit
ITT Population

Parameter	Statistic	Cariprazine (N=227)	Risperidone (N=229)	Overall (N=456)
Screening	N	227	229	456
	Mean	0.97	0.97	0.97
	Median	0.00	0.00	0.00
	Std. Dev.	1.350	1.277	1.312
	Min, Max	0.0, 6.0	0.0, 5.0	0.0, 6.0
Baseline	N	227	229	456
	Mean	0.72	0.86	0.79
	Median	0.00	0.00	0.00
	Std. Dev.	1.193	1.317	1.257
	Min, Max	0.0, 6.0	0.0, 6.0	0.0, 6.0

Outcomes and estimation

Primary endpoint

The primary efficacy parameter was the change from baseline to endpoint in the PANSS factor score for negative symptoms. The primary analysis was performed using an MMRM with treatment group, pooled study centre, visit, and treatment group-by visit interaction as fixed effects and the baseline value and baseline value-by –visit interaction as the covariates. The unstructured covariance matrix was allowed to be different for the 2 treatment groups. Using this model, there was a statistically significant difference in favour of cariprazine over risperidone (P=0.002)

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			

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, ITT=intent to treat, PANSS=Positive and Negative Symptom Scale

a The PANSS factor score for negative symptoms ranged from 7 to 49, a lower score was favorable.

b This analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values.

** Cariprazine was statistically significant compared with risperidone, $P < 0.01$.

Table 25. Summary statistics for the change from baseline in the PANSS factor score for negative symptoms at each follow-up assessment (observed and LOCF)-ITT-population

	Cariprazine (N=227)			Risperidone (N=229)		
Week	n	Mean ± SD [a,b]	Mean CFB (95% CI)	n	Mean ± SD [a,b]	Mean CFB (95% CI)
0	227	27.7 ± 2.6	NA	229	27.5 ± 2.4	NA
Observed						
1	227	26.7 ± 2.8	-1.1 (-1.3, -0.9)	227	26.5 ± 2.8	-1.0 (-1.2, -0.7)
2	223	25.3 ± 3.2	-2.5 (-2.8, -2.1)	225	25.2 ± 3.1	-2.2 (-2.6, -1.9)
3	219	24.0 ± 3.7	-3.7 (-4.1, -3.3)	224	24.1 ± 3.8	-3.4 (-3.8, -2.9)
4	217	23.0 ± 4.0	-4.7 (-5.2, -4.3)	219	23.2 ± 3.8	-4.2 (-4.7,-3.7)
6	213	22.2 ± 4.0	-5.5 (-6.0, -5.0)	212	22.2 ± 3.9	-5.1 (-5.7, -4.6)
10	203	21.1 ± 4.3	-6.6 (-7.2, -6.0)	204	21.3 ± 4.1	-6.0 (-6.6, -5.5)
14	185	19.9 ± 4.6	-7.8 (-8.4, -7.1)	197	20.8 ± 4.6	-6.6 (-7.3, -6.0)
18	182	19.3 ± 4.5	-8.4 (-9.1, -7.8)	189	20.4 ± 4.6	-7.1 (-7.7, -6.4)
22	178	18.8 ± 4.6	-9.0 (-9.6, -8.3)	182	19.9 ± 4.8	-7.6 (-8.3, -6.9)
26	175	18.5 ± 4.7	-9.3 (-10.0, -8.6)	178	19.6 ± 5.1	-7.9 (-8.7, -7.1)
LOCF						
1	227	26.7 ± 2.8	-1.1 (-1.3, -0.9)	229	26.5 ± 2.8	-1.0 (-1.2, -0.7)
2	227	25. 3 ± 3.2	-2.4 (-2.7, -2.1)	229	25.2 ± 3.1	-2.2 (-2.6, -1.9)
3	227	24.1 ± 3.7	-3.6 (-4.0, -3.2)	229	24.1 ± 3.8	-3.4 (-3.8, -2.9)
4	227	23.1 ± 4.0	-4.6 (-5.1, -4.1)	229	23.4 ± 3.8	-4.1 (-4.5,-3.6)
6	227	22.4 ± 4.0	-5.3 (-5.8, -4.8)	229	22.6 ± 4.1	-4.9 (-5.4, -4.3)
10	227	21.5 ± 4.4	-6.3 (-6.8, -5.7)	229	21.8 ± 4.4	-5.7 (-6.2, -5.1)
14	227	20.6 ± 4.8	-7.1 (-7.7, -6.5)	229	21.4 ± 4.8	-6.1 (-6.7, -5.5)
18	227	20.1 ± 4.9	-7.6 (-8.2, -7.0)	229	21.1 ± 4.9	-6.4 (-7.0, -5.7)
22	227	19.8 ± 4.9	-8.0 (-8.6, -7.4)	229	20.8 ± 5.1	-6.7 (-7.4, -6.0)
26	227	19.5 ± 5.0	-8.2 (-8.9, -7.6)	229	20.5 ± 5.3	-6.9 (-7.6, -6.2)

Abbreviations: CFB=change from baseline; CI=confidence interval; ITT=intent to treat; LOCF=last observation carried forward; N=number of patients overall; n (%)=number and percent of patients in the sample; NA=not applicable, PANSS=Positive and Negative Syndrome Scale

a The PANSS factor score for negative symptoms ranged from 7 to 49, a lower score was favorable.

b This analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values. For the LOCF analysis, for patients who terminated early the last observed score (obtained on the early termination visit) was carried forward to all subsequent scheduled assessments, up to Week 26.

Source: Table 14.2.1.8.1

Secondary endpoint

The secondary efficacy parameter was the change from baseline to week 26 in the PSP score analysed using an MMRM and a statistically significant difference (P=0.001) in favour of cariprazine was found.

Table 26. Repeated measures ANCOVA mixed-effects model on the change from baseline to week 26 in the PSP score, 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 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			

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent to treat; PSP=Personal and Social Performance scale

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

b This analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values.

** Cariprazine was statistically significant compared with risperidone, $P < 0.01$.

*** Cariprazine was statistically significant compared with risperidone, $P < 0.001$.

Table 27. Summary statistics for the change from baseline in the PSP score at each follow-up assessment (observed and LOCF) – ITT population

	Cariprazine (N=227)			Risperidone (N=229)		
Week	n	Mean ± SD [a, b]	Mean CFB (95% CI)	N	Mean ± SD [a, b]	Mean CFB (95% CI)
0	227	48.8 ± 10.9	NA	229	48.1 ± 10.72	NA
Observed						
6	218	54.8 ± 11.6	6.0 (5.0, 7.0)	225	53.1 ± 13.2	5.1 (3.9, 6.2)
10	203	57.5 ± 11.7	8.7 (7.5, 9.9)	204	55.4 ± 12.9	7.3 (6.1, 8.6)
14	186	60.0 ± 11.2	11.0 (9.6, 12.4)	197	57.4 ± 13.6	9.2 (7.8, 10.6)
18	182	61.5 ± 11.3	12.4 (10.9, 13.9)	189	58.2 ± 13.4	10.0 (8.6, 11.4)
22	178	62.7 ± 11.2	13.9 (12.3, 15.6)	183	59.0 ± 13.5	10.7 (9.1, 12.2)
26	175	64.0 ± 10.8	15.1 (13.5, 16.8)	178	59.7 ± 13.7	11.5 (9.9, 13.1)
LOCF						
6	218	54.8 ± 11.6	6.0 (5.0, 7.0)	225	53.1 ± 13.2	5.1 (3.9, 6.2)
10	218	56.9 ± 11.8	8.1 (6.9, 9.3)	225	54.4 ± 13.5	6.4 (5.2, 7.6)
14	218	58.4 ± 11.9	9.7 (8.3, 11.0)	225	55.9 ± 14.1	7.8 (6.5, 9.2)
18	218	59.5 ± 12.3	10.7 (9.3, 12.1)	225	56.2 ± 14.2	8.2 (6.8, 9.6)
22	218	60.6 ± 12.5	11.8 (10.3, 13.3)	225	56.6 ± 14.2	8.5 (7.0, 10.0)
26	218	61.4 ± 12.4	12.6 (11.1, 14.2)	225	57.2 ± 14.5	9.1 (7.6, 10.6)

Abbreviations: CFB=change from baseline; CI=confidence interval; ITT=intent to treat; LOCF=last observation carried forward; N=number of patients overall; n (%)=number and percent of patients in the sample; NA=not applicable; PSP=Personal and Social Performance Scale

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

b This analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values. For the LOCF analysis, for patients who terminated early the last observed score (obtained on the early termination visit) was carried forward to all subsequent scheduled assessments, up to Week 26.

Ancillary analyses

The change from baseline in the CGI-S and the CGI-I scores were analysed using an MMRM analysis and a statistically significant difference (P=0.005 and P<0.001 respectively) in favour of cariprazine was seen at week 26.

The change in PANSS negative subscale score was statistically significant in favour of cariprazine (P=0.001) and the change in PANSS positive subscale and the PANSS general psychopathology scores were not statistically significant. The change from baseline in PANSS total score was not statistically significant using the same analyses.

The change from baseline in the PSP self-care using an MMRM a statistically significant difference (P=0-004) was seen in favour of cariprazine at week 26. In an analysis based on an ANCOVA model using the LOCF approach no statistically significant difference was seen. For the PSPs area socially useful activities and personal and social relationships scores statistically significant differences were seen for both areas using MMRM and ANCOVA model. The PSP area disturbing and aggressive behaviours did not show any statistically significant difference for neither the analysis.

A total of 157 cariprazine-treated patients (69.2%) achieved decreases of at least 20% in PANSS factor score for negative symptoms compared to 133 risperidone-treated patients (58.1%), and a statistically significant difference (P=0.002) in favour of cariprazine was seen.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28. Summary of efficacy for trial RGH-MD-04

Title: A DOUBLE-BLIND, PLACEBO AND ACTIVE-CONTROLLED EVALUATION OF THE SAFETY AND EFFICACY OF CARIPRAZINE IN THE ACUTE EXACERBATION OF SCHIZOPHRENIA			
Study identifier	RGH-MD-04		
Design	Multicenter, multinational, randomized, double-blind, placebo and active-controlled, parallel group, fixed-dose study in adult patients who had a primary diagnosis of schizophrenia		
	Duration of no-drug screening phase: Duration of main phase: Duration of safety follow-up phase:		Up to 7 days 6 weeks 2 weeks
Hypothesis	Superiority of flexible regimens of cariprazine compared to placebo		
Treatments groups	cariprazine (3mg)		Oral capsule. 6 weeks, 155 randomized patients
	cariprazine (6mg)		Oral capsule. 6 weeks, 157 randomized patients
	Aripiprazole 10mg		Oral capsule. 6 weeks, 152 randomized patients
	Placebo		Oral capsule. 6 weeks, 153 randomized patients
Endpoints and definitions	Primary endpoint (MMRM, mITT)	PANSS-T	Change from baseline to Week 6 in the PANSS total score in all patients with at least one post-baseline measurement, using a mixed effect model for repeated measures with treatment group, study center, visit and treatment group by visit interaction as covariates.
	Secondary endpoint (MMRM)	CGI-S	Change from baseline to week 6 in GCI-S score.
	Other endpoints (MMRM)	PANSS+ PANSS- CGI-I NSA-16 total score NSA Global Negative Symptom	Change from baseline at 6 weeks.
	(ANCOVA, LOCF)	SQLS-R4 total score, SQLS-R4 psychosocial score, SQLS-R4 vitality score	Change from baseline at 6 weeks, ANCOVA model including treatment group and study centers as factors and baseline score as a covariate. LOCF for missing data.
	(Logistic model)	Proportion of responders (with 30% or greater reduction)	The proportion of patients achieving clinical improvement on the PANSS-T at 6 weeks. Treatment and baseline as explanatory variables in the Logistic model.

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Primary analysis at the end of the 6 weeks of double-blind treatment, based on the ITT dataset.				
PANSS-T change from Baseline to endpoint (6 weeks/ MMRM).	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Number of subject	151	154	149	150
		Week 6			
	Change Mean (SE)	–20.2 (1.5)	–23.0 (1.5)	–14.3 (1.5)	-21.2 (1.4)

	Treatment differences against placebo (LS Mean)	-6.0	-8.8		-7
	95% CI	[−10.1, −1.9]	[−12.9, −4.7]		[−11.0, −2.9]
	P value	0.0044	< 0.0001		0.0008
Analysis description	**Secondary Analysis**				
CGI-S change from Baseline to endpoint (6 weeks/ MMRM),	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Change mean (SE)	−1.4 (0.1)	−1.5 (0.1)	−1.0 (0.1)	−1.4 (0.1)
	Treatment differences against placebo LS Mean	-0.4	-0.5		-0.4
	95% CI	[−0.6, −0.2]	[−0.7,-0.3]		[−0.6,-0.2]
	p-value	0.0004	< 0.0001		0.0001
Analysis description	**Additional Analysis**				
PANSS + change from Baseline to endpoint (6 weeks/MMRM),	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Change mean (SE)	−6.8 (0.5)	−7.5 (0.5)	−5.3 (0.5)	−7.2 (0.4)
	Treatment differences against placebo LS Mean	−1.5	−2.2		−1.9
	95% CI	(−2.8,−0.2)	(−3.5,−0.9)		(−3.1,−0.6)
	p-value	0.0258	0.0009		0.0038
PANSS - change from Baseline to endpoint (6 weeks/MMRM),	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Change mean (SE)	−4.4 (0.4)	−4.7 (0.4)	−3.0 (0.4)	−4.2 (0.3)
	Treatment differences against placebo LS Mean	−1.4	-1.7		−1.2
	95% CI	(−2.4,−0.4)	(−2.7,−0.7)		(−2.2,−0.2)
	p-value	0.0068	0.0009		0.0152
CGI-I change from Baseline to endpoint (6 weeks/ MMRM),	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Change mean (SE)	2.7 (0.1)	2.7 (0.1)	3.2 (0.1)	2.7 (0.1)
	Treatment differences against placebo LS Mean	-0.6	-0.5		−0.5
	95% CI	(−0.9, −0.3)	(−0.8,−0.2)		(−0.8,−0.3)
	p-value	0.0001	0.0004		0.0003
NSA-16 Global Negative Symptoms	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Change mean (SE)	−0.5 (0.1)	−0.6 (0.1)	−0.3 (0.1)	−0.6 (0.1)
	Treatment differences against placebo LS Mean	−0.3	−0.3		−0.3
	95% CI	(−0.4,−0.1)	(−0.5,−0.1)		(−0.5,−0.1)
	p-value	0.0060	0.0008		0.0005
NSA-16 Total score	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)

	Change mean (SE)	−6.6 (0.8)	−7.5 (0.8)	−3.0 (0.8)	−7.2 (0.8)
	Treatment differences against placebo LS Mean	−3.6	−4.5		−4.2
	95% CI	(−5.8, -1.3)	(−6.7, −2.3)		(−6.4,−2.0)
	p-value	0.0018	< 0.0001		0.0002
Schizophrenia Quality of Life Scale Total score Revision 4 SQLS-R4 (LOCF, mITT)	Treatment group	Cariprazine (3 mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Change mean (SE)	−9.9 (1.6)	−11.5 (1.6)	−3.1 (1.6)	−12.8 (1.6)
	Treatment differences against placebo LS Mean	-6.8	−8.3		−9.7
	95% CI	(−11.2, −2.4)	(−12.7, −4.0)		(−14.0, -5.3)
	p-value	0.0027	0.0002		< 0.0001
PANSS responders (≥30% improvement in PANSS total score at Week 6 compared with baseline) LOCF mITT.	Treatment group	Cariprazine (3mg)	Cariprazine (6mg)	Placebo	Aripiprazole (10mg)
	Odds Ratio vs Placebo	1.36	1.96		1.80
	95% CI	(0.78, 2.35)	(1.15, 3.34)		(1.05, 3.09)
	p-value	0.2794	0.0127		0.0313

Table 29. Summary of efficacy for trial RGH-MD-05

Title: A DOUBLE-BLIND, PLACEBO-CONTROLLED EVALUATION OF THE SAFETY AND EFFICACY OF CARIPRAZINE IN THE ACUTE EXACERBATION OF SCHIZOPHRENIA			
Study identifier	RGH-MD-05		
Design	Multicenter, multinational, randomized, double-blind, placebo -controlled, parallel group, fixed/flexible-dose study in adult patients who had a primary diagnosis of schizophrenia		
	Duration of no-drug screening phase: Duration of main phase: Duration of safety follow-up phase:		Up to 7 days 6 weeks 2 weeks
Hypothesis	Superiority of flexible regimens of cariprazine compared to placebo		
Treatments groups	cariprazine (3-6 mg)		Oral capsule. 6 weeks, 151 randomized patients
	cariprazine (6-9 mg)		Oral capsule. 6 weeks, 148 randomized patients
	Placebo		Oral capsule. 6 weeks, 147 randomized patients
Endpoints and definitions	Primary endpoint (MMRM, mITT)	PANSS-T	Change from baseline to Week 6 in the PANSS total score in all patients with at least one post-baseline measurement, using a mixed effect model for repeated measures with treatment group, study center, visit and treatment group by visit interaction as covariates.
	Secondary endpoint (MMRM)	CGI-S	Change from baseline to week 6 in GCI-S score.

	Other endpoints (MMRM)	PANSS+ PANSS- CGI-I NSA-16 total score NSA Global Negative Symptom ; SQLS-R4 total and its sub-scores, CDR attention battery and CTT scores	Change from baseline at 6 weeks.
	(Logistic model)	Proportion of responders (with 30% or greater reduction)	The proportion of patients achieving clinical improvement on the PANSS-T at 6 weeks, with a logistic regression model using treatment and baseline as explanatory variables. LOCF for missing data.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Primary analysis at the end of the 6 weeks of double-blind treatment, based on the ITT dataset.			
PANSS-T change from Baseline to endpoint (6 weeks/ MMRM).	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Number of subject	147	147	145
		Week 6		
	Change Mean (SE)	–22.8 (1.6)	–25.9 (1.7)	–16.0 (1.6)
	Treatment differences against placebo (LS Mean)	-6.8	-9.9	
	95% CI	[–11.3, –2.4]	[–14.5, –5.3]	
	P value	0.0029	< 0.0001	

Analysis description	**Secondary Analysis**			
CGI-S change from Baseline to endpoint (6 weeks/ MMRM),	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Change mean (SE)	–1.4 (0.1)	–1.6 (0.1)	–1.0 (0.1)
	Treatment differences against placebo LS Mean	-0.3	-0.5	
	95% CI	[–0.6, –0.1]	[–0.8,-0.3]	
	p-value	0.0115	< 0.0001	

Analysis description	**Additional Analysis**			
PANSS + change from Baseline to endpoint (6 weeks/MMRM),	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Change mean (SE)	–7.8 (0.5)	–9.1 (0.6)	–5.8 (0.6)
	Treatment differences against placebo LS Mean	-2.0	-3.4	
	95% CI	[–3.5, –0.6]	[–4.9, –1.8]	
	p-value	0.0074	< 0.0001	
PANSS - change from Baseline to endpoint (6 weeks/MMRM),	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Change mean (SE)	–4.3 (0.4)	–5.0 (0.5)	–3.4 (0.5)

	Treatment differences against placebo LS Mean	-0.9	-1.7	
	95% CI	[−2.1, 0.3]	[−2.9, −0.4]	
	p-value	0.1548	0.0095	
CGI-I change from Baseline to endpoint (6 weeks/ MMRM),	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Change mean (SE)	2.6 (0.1)	2.4 (0.1)	3.2 (0.1)
	Treatment differences against placebo LS Mean	-0.6	-0.9	
	95% CI	[−0.9, −0.3]	[−1.2,−0.5]	
	p-value	0.0003	< 0.0001	
NSA-16 Total score	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Change mean (SE)	−8.0 (0.9)	−9.1 (0.9)	−5.6 (1.0)
	Treatment differences against placebo LS Mean	−2.4	−3.4	
	95% CI	[−4.9, 0.1]	[−6.0, −0.9]	
	p-value	0.0649	0.0089	
NSA Global Negative Symptom Rating	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Change mean (SE)	−0.6 (0.1)	−0.6 (0.1)	−0.5 (0.1)
	Treatment differences against placebo LS Mean	−0.2	−0.2	
	95% CI	[−0.4, 0.0]	[−0.4, 0.0]	
	p-value	0.0862	0.1193	
PANSS 30% responders (6 weeks/LOCF), mITT.	Treatment group	Cariprazine (3-6 mg)	Cariprazine (6-9 mg)	Placebo
	Odds Ratio vs Placebo	1.20	1.60	
	95% CI	[0.71, 2.03]	[0.96, 2.67]	
	p-value	0.4844	0.0696	

Table 30. Summary of efficacy for trial RGH-MD-16

Title: EVALUATION OF THE SAFETY AND EFFICACY OF RGH-188 IN THE ACUTE EXACERBATION OF SCHIZOPHRENIA		
Study identifier	RGH-MD-16	
Design	Multicenter, multinational, randomized, double-blind, placebo and active-controlled, parallel group, fixed-dose study in adult patients who had a primary diagnosis of schizophrenia	
	Duration of no-drug screening phase: Duration of main phase: Duration of safety follow-up phase:	Up to 7 days 6 weeks 2 weeks
Hypothesis	Superiority of fixed regimens of cariprazine compared to placebo	
Treatments groups	cariprazine 1.5 mg	Oral capsule. 6 weeks, 145 randomized patients
	cariprazine 3 mg	Oral capsule. 6 weeks, 147 randomized patients
	cariprazine 4.5 mg	Oral capsule. 6 weeks, 148 randomized patients
	risperidone 4 mg	Oral capsule. 6 weeks, 141 randomized patients

	placebo		Oral capsule. 6 weeks, 151 randomized patients			
Endpoints and definitions	Primary endpoint (LOCF, mITT)	PANSS-T	Change from baseline to Week 6 in the PANSS total score in all patients with at least one post-baseline measurement, using a mixed effect model for repeated measures with treatment group, study center, visit and treatment group by visit interaction as covariates.			
	Secondary endpoint (LOCF)	CGI-S	Change from baseline to week 6 in GCI-S score.			
	Other endpoints (LOCF)	PANSS+ PANSS- CGI-I NSA-16 total score NSA Global Negative Symptom	Change from baseline at 6 weeks.			
	(Logistic model)	Proportion of responders (with 30% or greater reduction)	The proportion of patients achieving clinical improvement on the PANSS-T at 6 weeks. Treatment and baseline as explanatory variables in the Logistic model.			
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Primary analysis at the end of the 6 weeks of double-blind treatment, based on the ITT dataset.					
PANSS-T change from Baseline to endpoint (6 weeks/ LOCF)	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Number of subject	140	140	145	148	138
		Week 6				
	Change Mean (SE)	−17.3 (1.7)	−18.7 (1.8)	−20.2 (1.6)	-9.5 (1.6)	-25.3 (1.7)
	Treatment differences against placebo (LS Mean)	-7.5	-8.8	-10.4		-15.0
	95% CI	−11.8, −3.3	−13.1, −4.6	-14.6, -6.2		−19.4, −10.8
	P value	0.0005	< 0.0001	< 0.0001		< 0.0001
Analysis description	**Secondary Analysis**					
CGI-S change from Baseline to endpoint (6 weeks/ LOCF)	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Change mean (SE)	-0.9 (0.1)	-1.1 (0.1)	-1.2 (0.1)	-0.6 (0.1)	-1.4 (0.1)
	Treatment differences against placebo (LS Mean)	-0.4	-0.5	-0.6		-0.8
	95% CI	-0.6, -0.1	-0.7, -0.2	-0.9, -0.4		-1.1, -0.6
	p-value	0.0040	0.0003	< 0.0001		< 0.0001
Analysis description	**Additional Analysis**					
PANSS + change from Baseline to endpoint (6	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Baseline mean (SE)	25.2 (0.3)	25.5 (0.3)	25.5 (0.3)	25.4 (0.3)	25.5 (0.3)

weeks/ LOCF)	Treatment differences against placebo LS Mean	-2.0	-2.9	-3.4		-5.4
	95% CI	-3.4, -0.6	-4.3, -1.5	-4.8, -2.0		-6.8, -3.9
	p-value	0.0056	< 0.0001	< 0.0001		< 0.0001
PANSS - change from Baseline to endpoint (6 weeks/ LOCF)	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Baseline mean (SE)	24.3 (0.4)	24.5 (0.4)	24.5 (0.4)	25.2 (0.4)	25.2 (0.4)
	Treatment differences against placebo LS Mean	-2.2	-2.5	-3.0		-3.1
	95% CI	-3.2, -1.1	-3.5, -1.4	-4.0, -2.0		-4.2, -2.1
	p-value	< 0.0001	< 0.0001	< 0.0001		< 0.0001
CGI-I change from Baseline to endpoint (6 weeks/ LOCF, ANCOVA)	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Treatment differences against placebo LS Mean	-0.5	-0.6	-0.8		-1.0
	95% CI	-0.8, -0.2	−0.9, −0.3	−1.1, −0.5		−1.3, −0.7
	p-value	0.0012	< 0.0001	< 0.0001		< 0.0001
NSA-16 Global Negative Symptoms	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Baseline mean (SE)	4.1 (0.1)	4.0 (0.1)	4.0 (0.1)	4.1 (0.1)	4.1 (0.1)
	Treatment differences against placebo LS Mean	-0.2	-0.3	-0.3		-0.4
	95% CI	-0.4, -0.1	-0.5, -0.1	-0.5, -0.1		-0.6, -0.2
	p-value	0.0097	0.0029	0.0009		0.0001
NSA-16 Total score	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Baseline mean (SE)	55.2 ± 1.0	56.0 ± 1.0	54.9 ± 0.9	55.9 ± 0.9	55.5 ± 1.1
	Treatment differences against placebo LS Mean	−3.9	−4.6	−5.5		−5.9
	95% CI	−6.1, −1.7	−6.8, −2.4	−7.6, −3.3		−8.1, −3.7
	p-value	0.0005	< 0.0001	< 0.0001		< 0.0001
PANSS responders (≥30% improvement in PANSS total score at Week 6 compared with baseline) LOCF mITT.	Treatment group	Cariprazine (1.5 mg)	Cariprazine (3 mg)	Cariprazine (4.5 mg)	Placebo	Risperidone (4 mg)
	Odds Ratio vs Placebo	2.0	2.4	2.4		3.3
	95% CI	1.1, 3.4	1.4, 4.1	1.4, 4.1		1.9, 5.6
	p-value	0.015	0.002	0.001		< 0.001

Table 31. Summary of efficacy for trial RGH-MD-03

Title: A Double-Blind Placebo-Controlled Evaluation of the Safety and Efficacy of RGH-188 in the Acute exacerbation of Schizophrenia	
Study identifier	RGH-MD-03
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible dose, 10-week study in adults with a primary diagnosis of schizophrenia

	Duration of wash-out: Duration of main phase: Duration of extension phase:		Up to 7 days 6 weeks 4 weeks
Hypothesis	Superiority of flexible regimens of cariprazine compared to placebo		
Treatments groups	Low dose cariprazine (1.5-4.5mg)		Oral capsule. 6 weeks, 127 randomized patients
	High dose cariprazine (6-12mg)		Oral capsule. 6 weeks, 133 randomized patients
	Placebo		Oral capsule. 6 weeks, 129 randomized patients
Endpoints and definitions	Primary endpoint (ANCOVA, LOCF, mITT)	PANSS-T	Change from baseline to week 6 on the comparison between any cariprazine regimen and placebo in all patients with at least one post-baseline measurement, LOCF for missing values. Hierarchically, the single treatment arms are tested against placebo if the overall comparison is significant.
	Secondary endpoint (two-way ANCOVA)	CGI-S	Change from baseline to week 6 on the comparison between any cariprazine regimen and placebo in all patients with at least one post-baseline measurement.
	Other endpoints (ANCOVA)	PANSS+ PANSS- BPRS CDSS	Change from baseline at 6 weeks.
	(Logistic model)	Proportion of responders (with 20% or greater reduction)	The proportion of patients achieving clinical improvement on the PANSS-T at 6 weeks.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Primary analysis at the end of the 6 weeks of double-blind treatment, based on the mITT dataset (i.e. all patients with at least one post-baseline measurement), and LOCF for the missing data. It employed an ANCOVA model (including treatment, center and baseline).			
PANSS-T change from Baseline to endpoint (6 weeks/LOCF), ANCOVA, mITT.	Treatment group	Low Dose Cariprazine	High Dose Cariprazine	Placebo
	Number of subject	126	122	129
		Week 6		
	Change ± SEM	-13.48 ± 1.72	-14.81 ± 1.75	-9.81 ± 1.71
	p-value for the comparison of "any active arm" vs. "placebo" = 0.1			
	Treatment differences against placebo			
	LS Mean	-4.79	-2.88	
	95% CI	[-9.19, -0.38]	[-7.25, 1.48]	
	p-value	0.033	0.195	

	Secondary Analysis			
CGI-S change from Baseline to endpoint (6 weeks/LOCF),	Treatment group	Low Dose Cariprazine	High Dose Cariprazine	Placebo
	Change ± SEM	-0.73 ± 0.09	-0.69 ± 0.09	-0.58 ± 0.09

two-way ANCOVA, mITT.	p-value for the comparison of "any active arm" vs. "placebo" = 0.508			
	Treatment differences against placebo			
	LS Mean	0.14	0.07	
	95% CI	[-0.36, 0.09]	[-0.29, 0.16]	
	p-value	0.245	0.562	
PANSS+ change from Baseline to endpoint (6 weeks/LOCF), ANCOVA, mITT.	Change ± SEM	25.97 ± 0.34	25.98 ± 0.33	26.19 ± 0.33
	Treatment differences against placebo			
	LS Mean	-1.30	-0.99	
	95% CI	[-2.68, 0.08]	[-2.35, 0.37]	
	p-value	0.065	0.152	
PANSS- change from Baseline to endpoint (6 weeks/LOCF), ANCOVA, mITT.	Change ± SEM	22.87 ± 0.42	23.24 ± 0.40	22.32 ± 0.43
	Treatment differences against placebo			
	LS Mean	-1.35	-0.44	
	95% CI	[-2.55, -0.15]	[-1.62, 0.74]	
	p-value	0.027	0.464	
BPRS change from Baseline to endpoint (6 weeks/LOCF), ANCOVA, mITT.	Change ± SEM	-8.92 ± 1.02	-8.35 ± 1.04	-6.32 ± 1.03
	Treatment differences against placebo			
	LS Mean	-2.60	-1.74	
	95% CI	[-5.30, 0.09]	[-4.40, 0.92]	
	p-value	0.058	0.200	
CDSS change from Baseline to endpoint (6 weeks/LOCF), ANCOVA, mITT.	Change ± SEM	-0.86 ± 0.29	-1.67 ± 0.30	-0.39
	Treatment differences against placebo			
	LS Mean	-0.22)	-0.49	
	95% CI	[-0.94, 0.49]	[-1.20, 0.21]	
	p-value	0.537	0.169	
PANSS 20% responders (6 weeks/LOCF) two-way ANCOVA, mITT.	(%)	52	45	39
	p-value for the comparison of "any active arm" vs. "placebo" = 0.159			
	Treatment differences against placebo			
	Odds ration (CI)	1.64 (0.97, 2.76)	1.15 (0.68, 1.95)	
	p-value	0.065	0.602	

Table 32. Summary of efficacy for trial RGH-MD-06

A Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study of Cariprazine (RGH-188) in the Prevention of Relapse in Patients With Schizophrenia	
Study identifier	RGH-MD-06

Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible- and fixed-dose study evaluating time to relapse in adult patients who had a primary diagnosis of schizophrenia and had received cariprazine in the open-label phase (OLP) of the study. Patients were allowed to progress from run-in to stabilisation and from stabilisation to double-blind (see below) only if responders and tolerators.		
	Duration of screening phase: Duration of open-label run-in: Duration of open label stabilization phase: Duration of the double blind-phase: Duration of the safety follow-up:		1 week 8 weeks (6 flexible dose + 2 fixed dose) 12 weeks Variable (from 26 to 72 weeks) 4 weeks
Hypothesis	Superiority of cariprazine compared to placebo in prevention of relapses in patients that responded to and tolerated cariprazine.		
Treatments groups for the double blind phase	Cariprazine (3, 6, or 9 mg/day)		Oral capsule, on the dose fixed during the stabilisation phase. 101 patients randomised
	Placebo		Oral capsule. 99 patients randomised
Endpoints and definitions	Primary endpoint (logrank, mITT)	Time to first relapse in the double-blind phase	Relapse defined as any of the followings: 1. Psychiatric hospitalisation 2. Increase in PANSS by ≥30% for patients with ≥50 at baseline or by ≥10 points in patients who scored <50.* 3. Increase in CGI-S by ≥2 at Visit 14.* 4. Deliberate self-injury or violent behaviour 5. Significant suicidal or homicidal ideation 6. > 4 at any of the following PANSS items: P1, P2, P3, P6, P7, G8 or G14.* *if confirmed at a repeat visit within 7 days

Results and Analysis for the Double-blind phase

Time to First Relapse – ITT double-blind population (i.e. responders and tolerators in the previous phases)	Treatment group	Placebo	Cariprazine (3, 6, or 9 mg/day)
	Randomised (n)	99	101
	Censored (n)	52	76
	Events (n)	47	25
	Time to relapse in days (95% CI based on the KM estimates) (Patients who did not meet relapse criteria are considered censored at the time of completion or discontinuation)		
	25^{th} percentile	92 (44, 151)	224 (99, -)
	50^{th} percentile	296 (157, -)	-

	75th percentile	-	-
	p-value for superiority of cariprazine vs placebo using logrank test = 0.001		
	Hazard ratio (95%CI) for cariprazine vs placebo using Cox proportional hazards model: 0.45(0.28, 0.73)		

Table 33. Summary of efficacy for trial RGH-188-005

A randomized, double-blind, parallel-group study to investigate the efficacy, safety, and tolerability of cariprazine in patients with predominant negative symptoms of schizophrenia.			
Study identifier	RGH-188-005		
Design	Multicenter, randomized, double-blind, active-controlled, parallel-group, fixed/flexible dose, 26-week study in adults with a primary diagnosis of schizophrenia and with predominant negative symptoms		
	Duration of lead-in: Duration of double-blind: Duration of safety follow-up:		4 weeks 26 weeks (2 of up-titration + 24 of continuation) 2 weeks
Hypothesis	Superiority of a fixed/flexible regimen of cariprazine compared to risperidone in the reduction of negative symptoms.		
Treatments groups	Cariprazine (4.5mg, range 3-6)		Oral capsule, fixed dose with flexibility, 230 patients randomised
	Risperidone (4mg, range 3-6)		Oral capsule. fixed dose with flexibility, 231 patients randomised
Endpoints and definitions	Primary endpoint (MMRM, mITT)	PANSS factor score for negative symptoms	Change from baseline to week 26 on the comparison between cariprazine and risperidone in all patients with at least one post-baseline measurement.
	Secondary endpoint (MMRM, mITT)	Personal and Social Performance Scale (PSP)	Change from baseline to week 26 on the comparison between cariprazine and risperidone in all patients with at least one post-baseline measurement.
	Other endpoints (MMRM, mITT)	CGI-S CGI-I PANSS total score	Change from baseline at 6 weeks on the comparison between cariprazine and risperidone in all patients with at least one post-baseline measurement.
	(Logistic regression)	20% responders on the PANSS factor score for negative symptoms	Logistic regression with treatment group and center and baseline score as explanatory variables.
	Pseudo-specificity assessment (MMRM, mITT)	PANNS factor for positive symptoms; Calgary Depression Scale for Schizophrenia (CDSS)	Change from baseline to week 26 on the comparison between cariprazine and risperidone in all patients with at least one post-baseline measurement.
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Primary analysis at the end of the 26 weeks of double-blind treatment, based on the mITT dataset (i.e. all patients with at least one post-baseline measurement). It used an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as the covariates..		
PANSS Factor Score for Negative Symptoms change from Baseline to endpoint	Treatment group	Cariprazine	Risperidone
		Week 26	
	Change ± SE	-8.9 ± 0.3	-7.4 ± 0.4
	p-value for superiority of cariprazine vs risperidone = 0.002		
Secondary Analysis			
PSP change from Baseline to endpoint	Treatment group	Cariprazine	Risperidone
	Change ± SE	-14.3 ± 0.6	-9.7 ± 0.8
	p-value for superiority of cariprazine vs risperidone < 0.001		
CGI-S change from Baseline to endpoint.	Change	-0.9	-0.7
	Mean difference (95% CI): -0.2(-0.4, -0.1)		
	p-value for superiority of cariprazine vs risperidone = 0.005		
CGI-I change from Baseline to endpoint	Change	2.5	2.9
	Mean difference (95% CI): -0.4(-0.6, -0.2)		
	p-value for superiority of cariprazine vs risperidone < 0.001		
PANSS total score change from Baseline to endpoint	Change	-16.9	-14.8
	Mean difference (95% CI): -2.1(-4.3, 0.1)		
	p-value for superiority of cariprazine vs risperidone = 0.065		
PANSS factor for negative symptoms 20% responders (6 weeks/LOCF)	(%)	69.2	58.1
	p-value for superiority of cariprazine vs risperidone = 0.002		
Pseudospecificity assessment			
PANSS Factor Score for Positive Symptoms change from Baseline to endpoint	Change	-0.7	-0.8
	Difference between cariprazine vs risperidone (95% CI): -0.4, 0.5		
CDSS change from Baseline to endpoint	Change	-0.3	-0.2
	Difference between cariprazine vs risperidone (95% CI): -0.3, 0.2		

Extrapolation of Data to the EU Population

Short-term efficacy study population consisted of 2,131 patients with schizophrenia, of whom 664 (31%) were from European countries (Romania (67), Russia (340), and Ukraine (257)). Approximately, one-third of the patients from studies RGH-MD-04 and RGH-MD-16 and half of the patients for study RGH-MD-05 were enrolled at centres from the United States, South American, South African and Asian

study centres. When analysing the data, specific analyses were performed to show that the gained foreign clinical data is representative for the EU population:

The following region definitions were applied during the analyses.

• European Union (EU): member states of the European Union

• Europe: geographic Europe including EU member states, Russia, Serbia and Ukraine

• European-non-EU: Russia, Serbia and Ukraine (geographic Europe excluding EU member states)

Study RGH-188-005 in patients with predominant negative symptoms of schizophrenia was conducted solely in Europe. A subgroup analysis by region was performed with the aim of showing that cariprazine is an "ethnically insensitive" drug, meaning unlikely to behave differently in different populations. Regions in the analysis were EU versus European-non-EU countries. As the subgroup analysis of regions demonstrated, there was no clinically meaningful difference in the CFB to Week 26 in the primary efficacy parameter.

Study RGH-MD-06 was performed in the US, India, Ukraine, Slovakia and Romania. In the cariprazine group during the double-blind phase 19 patients came from Romania and Slovakia (EU), whereas 38.6% (39/101) were from Eastern Europe i.e. Ukraine. As medical practice in Eastern European countries is very much comparable to medical practice in Ukraine and Russia, subgroup analyses were performed using the geographic region of Europe including Romania, Slovakia and Ukraine. The rate of relapse was similar for the European subgroup (Romania, Slovakia and Ukraine) p=0.005 and for the non-European (US, India) subgroup p=0.04; however the time to relapse was significantly longer for the non-European compared to the European subgroup. Additionally, the hazard ratio vs. placebo was better for the European population than for the non-European population (0.36 and 0.53, respectively). Further analyses were performed dividing the non-European subgroup into US and Asia. European and Asian patients showed the best relapse rates, while US patients the worst.

Subgroup analyses by region were performed for Studies RGH-MD-04 and RGH-MD-16 only, since the other two short-term studies (RGH-MD-05, RGH-MD-03) did not have patients from Europe.
Improvement in the PANSS total score was similar in both the European and the non-European population in the cariprazine groups, with the exception of the non-European patients in the cariprazine 3 mg/day group in Study RGH-MD-04 the difference over placebo was not statistically significant.

Table 3.3.1-4 Change From Baseline to Week 6 in the PANSS Total Score (LOCF) in the Confirmatory Studies, by Geographic Region—ITT Populations

	Fixed-Dose Studies								
	RGH-MD-04				*RGH-MD-16*				
	Placebo (N = 149)	Cariprazine		Aripiprazole 10 mg/day (N = 150)	Placebo (N = 148)	Cariprazine			Risperidone 4 mg/day (N = 138)
		3 mg/day (N = 151)	*6 mg/day (N = 154)*			*1.5 mg/day (N = 140)*	*3 mg/day (N = 140)*	*4.5 mg/day (N = 145)*	
Europe									
n	**97**	**98**	**101**	**97**	**58**	**56**	**53**	**54**	**50**
Baseline PANSS total score, mean ± SD	97.7±9.1	97.1±8.9	95.5±9.4	96.5±8.7	96.3±9.4	96.5±8.8	97.4±8.3	96.5±9.2	98.6±8.1
Change at Week 6, mean ± SD	-8.9±17.2	-18.1±17.7	-20.2±17.5	-18.7±17.7	-14.2±20.4	-16.4±18.0	-19.3±17.5	-21.6±16.0	-22.0±15.0
Difference in Change, mean (SE)[a]	-	-9.2(2.5)	-11.3(2.5)	-9.8(2.5)	-	-2.2(3.6)	-5.1(3.6)	-7.4(3.5)	-7.8(3.5)
Non-Europe									
n	**52**	**53**	**53**	**53**	**90**	**84**	**87**	**91**	**88**
Baseline PANSS total score, mean ± SD	94.2±8.6	94.1±8.1	96.0±9.3	94.0±9.4	98.0±9.1	97.5±9.4	97.1±8.9	96.8±8.9	97.9±10.3
Change at Week 6, mean ± SD	-15.7±19.3	-13.8±18.1	-16.7±19.1	-18.8±16.9	-6.5±18.8	-17.9±22.2	-18.3±22.8	-19.4±20.6	-27.2±22.3
Difference in Change, mean (SE)[a]	-	1.8 (3.7)	-1.0(3.7)	-3.1(3.5)	-	-11.4(3.1)	-11.8(3.1)	-12.9(2.9)	-20.7(3.1)

a Difference in change at Week 6 for cariprazine minus placebo or active control minus placebo.
ITT = intent to treat; LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Scale

Clinical studies in special populations

The main studies described above, included patients up to the age of 60 years. The study RGH-MD-188-005 included patients up to 65 years of age.

STUDY A002-A7 A LONG-TERM STUDY OF MP-214 (CARIPRAZINE) IN PATIENTS WITH CHRONIC PHASE OR ELDERLY SCHIZOPHRENIA

This study was a multicentre, randomized, 48 week open-label, active (risperidone) controlled, parallel-group, flexible dose phase 3 study in Japanese adults and elderly with chronic phase or elderly schizophrenia. Long-term safety, tolerability and efficacy were to be studied. In elderly cariprazine group there were finally 17 patients (65-72 years) and in risperidone group 10 patients (65-70 years).

With regard to efficacy, descriptive statistic scores for the difference from the baseline after 48 weeks of treatment (LOCF) for most parameters were slightly worse in cariprazine group and slightly better in risperidone group (e.g. PANSS-total score worsened 4.6 ± 21.4 in cariprazine group and improved -2.8 ± 14.9 in risperidone group; CGI-S worsened 0.2 ± 1.1 in cariprazine group and improved -0.1 ± 1.1 in risperidone group). No conclusions can be made due to small number of patients. With regard to safety in elderly patients, although cariprazine treatment may have increased the incidence of adverse events such as schizophrenia or hypertension, adverse events leading to discontinuation among adverse events observed in several elderly patients in cariprazine group were schizophrenia (5/17 patients (29.7%)) and paranoia (2/17 patients (11.8%)); the corresponding figures for non-elderly patients were 16/66 patients (24.2%) for schizophrenia and 0/66 patients (0.0%) for paranoia. These figures are too small for any conclusions.

Only 17 patients over 65 years of age were included into this Japanese study in the cariprazine group; no patients >65 years of age were included into the other schizophrenia studies.

Supportive studies

Short-term efficacy

- RGH-MD-03: A Double-blind Placebo-Controlled Evaluation of the Safety and Efficacy of RGH-188 in the Acute Exacerbation of Schizophrenia.

Design

This was a Phase 2, multicentre, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study conducted in the United States. The study enrolled male and female inpatients (18 to 65 years) who met DSM-IV-TR criteria for schizophrenia and had a PANSS total score of ≥ 80 and ≤ 120, a PANSS item P1 (delusions) or P3 (hallucinatory behaviour) score of ≥ 4, and a PANSS item P2 (conceptual disorganization) or P6 (suspiciousness/ persecution) score of ≥ 4. Patients were randomized to 1 of 3 treatment arms: placebo, cariprazine 1.5 to 4.5 mg/day, or cariprazine 6 to 12 mg/day. After a no-drug washout period of up to 7 days, randomized patients entered the 6-week double-blind treatment period and received cariprazine or placebo. Patients randomized to the cariprazine groups received 1.5 mg/day on Days 1 and 2. For inadequate responders, the dose could have been raised in 1.5-mg or 1.5- to 3-mg increments to reach the maximum dose of 4.5 mg/day by Day 5 (1.5- to 4.5-mg/day group) or 12 mg/day by Day 9 (6- to 12-mg/day group), respectively, if there were no tolerability problems. After 6 weeks of double-blind treatment or premature discontinuation during the double-blind phase (DBP), patients were followed up for safety assessments for 4 weeks. During this period, patients received treatment at the discretion of the Investigator.

Results

The ITT Population included 377 patients (placebo, n = 126; cariprazine 1.5 to 4.5 mg/day, n = 122; cariprazine 6 to 12 mg/day, n = 129). Of the patients in the Safety Population, 53.7% (209/389) completed the 6 weeks of double-blind treatment. No statistically significant differences between cariprazine- and placebo-treated patients were observed with respect to the overall discontinuation rate or individual reason for discontinuation. The most frequent reasons for discontinuation were insufficient therapeutic response (17%), withdrawal of consent (14.4%), and AEs (10.5%).

The primary efficacy parameter was the CFB to Week 6 in the PANSS total score. The primary analysis was performed using an ANCOVA model with missing data imputed by the LOCF approach. A sensitivity analysis was performed using an MMRM model. No statistically significant improvement for the primary efficacy parameter (CFB to Week 6 in PANSS total score) in the cariprazine treatment groups relative to placebo based on the protocol-specified testing procedure was observed (Table 2.2.1-1). Discrepancy between OC and MMRM sensitivity analyses concerning primary efficacy parameter was observed.

The secondary efficacy parameter was the CFB to Week 6 in the CGI-S score. After 6 weeks of treatment, comparisons of each cariprazine dose with placebo demonstrated no significant improvement using LOCF or MMRM analyses.

Long-term efficacy

STUDY RGH-MD-11: EVALUATION OF THE LONG-TERM SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF CARIPRAZINE IN PATIENTS WITH SCHIZOPHRENIA

This was a multinational, multicentre, 48-week open-label, flexible-dose phase 3 study of cariprazine to primarily evaluate the long-term safety of cariprazine in patients with schizophrenia. This was an extension study: In addition to new participants, patients who completed the 6 week lead-in studies, i.e. RGH-MD-04 or RGH-MD-05, were recruited. The subjects received 48 weeks of open-label treatment with cariprazine dose from 3 - 9 mg single dose per day.

The efficacy measurements used were the PANSS, CGI-S scale, and PANSS responder rate, SQLS-R4, (CDR) System Attention Tests, and Colour Trails Test (CTT). PANSS and CGI-S decreased slightly over time also during extension phase supporting efficacy in the maintenance treatment. No decrease in efficacy was observed over the course of this long-term, open-label safety study. Approx. 70% of patients received cariprazine within the claimed posology (1.5-6mg/day).

STUDY RGH-MD-17: A LONG-TERM, OPEN-LABEL EXTENSION STUDY OF THE SAFETY AND TOLERABILITY OF RGH-188 (CARIPRAZINE) IN PATIENTS WITH SCHIZOPHRENIA

This was an international, multicentre, 48 week open-label, and flexible dose, outpatient extension phase 2 study of cariprazine 1.5-4.5 mg/day in order to primarily evaluate the long-term safety, tolerability and PK of cariprazine in patients with schizophrenia. This was an extension study where the enrolled population consisted of all patients who completed the lead-in study, RGH-MD-16.

Efficacy evaluations included PANSS (total, positive, negative and response (≥30% improvement in PANSS total)) and CGI-S scales. PANSS and CGI-S decreased slightly over time also during extension phase supporting efficacy in the maintenance. Results were well in line with results in study RGH-MD-11 with similar design. No decrease in efficacy was observed over the course of this long-term, open-label safety study.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

To demonstrate clinical efficacy, one exploratory (RGH-MD-03) and three confirmatory short-term studies (RGH-MD-04, RGH-MD-05 and RGH-MD-16), one long-term maintenance of effect study (RGH-MD-06), and one long-term negative symptom study (RGH-188-005) aiming at demonstrating efficacy in patients with predominate negative symptoms were provided. In addition, several supportive studies have been presented. Since no formal dose-response study was performed dose response relationship was primarily supported by the short term clinical trials, mainly RGH-MD-03 and RGH-MD-16. The latter study had fixed dose schedule and to support the dose response relationship by the pivotal short term studies is considered acceptable.

The sites were located in the US, in Europe, Colombia, South Africa, India and Malaysia. Whether the results from Eastern Europe and Russia can be extrapolated to Western Europe has been discussed. Only 3% of the patients in the short-term studies came from the EU and 30% from Europe including countries outside EU. Large differences in the change of PANSS between geographical areas in studies RGH-MD-04 and RGH-MD-16 were observed. The direction of the difference is contradictory between these two studies. This is of importance in evaluating efficacy and other possible differences between geographical areas and when extrapolating foreign data to the European population where marketing authorisation is intended for. The Applicant has appropriately described and discussed the suitability of extrapolation of results from clinical studies conducted outside the EU and in relation to similarities in standard medical care within the EU region.

All the studies included patients only with schizophrenia. Inclusion and exclusion criteria were identical in short-term studies RGH-MD-04 and RGH-MD-05, and very similar with RGH-MD-16, as well as with long-term maintenance of efficacy study RGH-MD-06, thus including adult patients with acute exacerbation of schizophrenia. The patients in the study RGH-188-005 were those with predominantly negative symptoms of schizophrenia. The primary efficacy analysis was based on the ITT population (ITT defined as "with one post-baseline assessment") in all confirmatory studies, which is appropriate. Allowed rescue medication was the same, and allowed concomitant medication was similar in these short- and long-term studies; however clarifications and discussion were provided on their use. The Applicant has discussed the significance of benzodiazepines in symptom control and benzodiazepine use in different treatment arms appropriately. The Applicant has also clarified specific antipsychotics or other prohibited psychotropic medication use in long-term efficacy studies.

The active controls included in the short-term efficacy trials, aripiprazole 10 mg/day and risperidone 4mg/day, are considered acceptable, and the doses are justified. The objective of these studies was not to show superiority or non-inferiority, therefore no formal comparison of cariprazine with these active controls was made. The used dose of aripiprazole 10 mg/day is the lowest within the recommended dose range and the dose of risperidone 4 mg/day is also within the recommended dose range for adults with schizophrenia; since these were fixed dose studies neither active control were allowed to be used at the maximum labelled dose, i.e. the dose may not have been optimal for all patients.

In the short term studies the discontinuation rate in all treatment arms are relatively large. Overall the discontinuation rates are between 30% and 40% in the placebo and cariprazine arms and slightly lower in the active control arms (risperidone and aripiprazole). The distribution among reasons for discontinuations is not dramatically different between the treatment arms although there is a higher rate of discontinuations due to insufficient therapeutic response in the placebo arms.

A history of substance abuse was reported frequently throughout the studies. However, urine drug screen and blood alcohol level were not checked that often and abuse might have occurred during the study unobserved and might have influenced the result. The applicant has discussed the rationale behind the schedule and even though a larger number of patients might have used alcohol or illicit drug during the study resulting in a larger dropout or inaccurate ratings, it is however unlikely that it would have influenced the results.

The main clinical studies did not enrol subjects with an age above 60 years with the exception of the study on negative symptoms, which enrolled patients up to 65 years old. The applicant used data from the RGH-188-005 study to perform an extrapolation from the efficacy at younger ages to elderly patients and concluded that, since there was no decline with age (up to 65 years) in the effect of cariprazine, it is expected that this effect is maintained also in the elderly. This is agreed. From an efficacy point of view, this is less of a concern but needs to be taken into account with respect to dose recommendations and safety and the overall B/R assessment for the elderly population with schizophrenia. The limitations in information concerning data from the elderly population has been included in the relevant sections of the SmPC.

In all of those studies, three different analyses treating missing data in different ways have been performed for continuous endpoints; MMRM, ANCOVA with LOCF and PMM. All those analyses show a consistency in results. MMRM and ANCOVA with LOCF answers the question of what would have happened if patients had stayed on randomised treatment. Given the high drop-out rate in the short term studies, a more conservative analysis using BOCF has been performed. For responder endpoints an analysis has been performed using LOCF for missing data. A conservative analysis on responder endpoints imputing non-responders for all missing data was performed and confirmed the results from the continuous endpoints.

In the short-term studies, the choice of primary and secondary efficacy parameters is supported. PANSS and CGI-S are frequently used, standardized and valid scales used as efficacy measures. There has been debate on minimal clinically significant difference (MCID) and extrapolation between measures and no final conclusions have been drawn (Hermes et al 2012, Levine et al 2008). However, PANSS responder rate is considered to reflect well the clinical relevance of the PANSS-scale findings. The PANSS responder is defined according to the current EMA guideline. A responder is defined as ≥30% improvement in PANSS, which is endorsed. In the CGI-S-score 1-point difference has been generally considered a clinically meaningful change (Busner et al, 2007). The acute treatment setting makes an evaluation of changes in negative symptoms in isolation from changes in other symptoms difficult to perform and the short-term duration may be too short in order to evaluate an effect on negative symptoms appropriately. Such an evaluation could only be supportive. These studies would not be appropriate for evaluating an effect on cognitive deficits either. It would require study duration of at least 6 months. However, to document the effect of treatment on cognitive function even if no specific indication is sought, for the purpose of characterizing the safety of the drug is endorsed.

In long-term studies the use of placebo to patients in need of active treatment is ethically problematic. However, using a randomised withdrawal study is recommended and the design is acceptable. Patients received either placebo (withdrawal) or cariprazine at the same dose (3, 6 or 9 mg/day) that they received during the stabilization phase. The dose range used in the study thus included also doses > 6mg/day, i.e. outside the claimed posology. The Applicant carried out a post-hoc analysis including only those doses within the claimed posology, which is acceptable taking into account the totality of data. A large number of patients in the active treatment groups is stated to have discontinued the study for "Other reasons". This seems mainly to be due to study closure and hence according to protocol. All discontinued patients have been censored in the primary analysis.

The predefined relapse criteria are well defined and are acceptable. CGI-S and I are rated and they are considered as global ratings. To include PSP as well is endorsed since it addresses a more specific rating of functional outcome. The analyses of the pooled short-term studies, the cariprazine 1.5-6.0-mg treatment group showed statistically significant improvement in PANSS-FSNS relative to placebo in change from baseline at Week 6. However, in order to rate NSA-16 a well predefined study population should be chosen. Since other required additional measures of potentially confounding

symptoms/diagnoses have not been taking into account, the potential improvement in negative symptoms should be assessed with caution.

The study on negative symptoms has been specifically designed in order to evaluate negative symptoms. Lack of a placebo group is justified by ethical concerns associated with long-term discontinuation of treatment in clinically stable patients. To evaluate changes in primary negative symptoms adequately, the changes should be in isolation from changes in other symptoms. To ensure that patients with true negative symptoms of schizophrenia are studied, and not those whose symptoms are related to depressive symptoms or extra-pyramidal symptoms (EPS), the EMA schizophrenia guideline states several inclusion and exclusion criteria that should be followed when designing the study. All these aspects have been considered by the applicant. Nevertheless other potentially confounding factors, such as anxiety, suicidality, cognitive dysfunction, hospitalization and environmental and other treatment and illness related factors could have been present. Some, but not all, above mentioned potentially confounding factors have been addressed through adding additional measures (suicidality, hospitalization). Cognitive impairment has not been addressed with a specific rating tool but was only rated through PANSS and since this factor also should be stable and not predominant during the trial, it is valuable to have specific measures of cognition as well. Anxiety was only rated through PANSS and not through a separate anxiety scale, e.g. the Hamilton anxiety scale which is a weakness since anxiety as well as other affective symptoms, could also confound the result.

There are different rating instruments to be used in trials of negative symptoms, PANSS subscale, PANSS negative factor, and SANS and NSA-16.They differ with respect to their domain coverage, use of informants, integration of a global score, administration time and comprehensiveness of their structured interviews. In the short-term studies NSA-16 was used. The applicant stated that the same approach was not used in the study concerning negative symptoms since scientific advice was sought from three European medicinal agencies on this issue. All three agencies stated that PANSS negative factor score would be preferable. In addition, in the EMA schizophrenia guideline two scales rating negative symptoms are mentioned, none of them is NSA-16. The applicant also states that PANSS is well known both by clinicians and companies. Even though a more specific scale rating negative symptoms would have been preferable, the applicants' reasoning is acceptable.

As secondary efficacy parameter the PSP score was used. This is endorsed since a possible improvement in negative symptoms and corresponding improvement in functioning would further strengthen the effect on negative symptoms. However, functional impairment can be driven by symptoms but also by other factors including many not related to the illness. Patients with negative symptoms would experience reduced range of emotions, social drive and interaction that may result in a life remote from society. It may also lead to difficulties in the overall treatment. Participating in a study per se would influence the result. However, this would affect any study performed regardless of the outcome and affect all treatment groups equally.

In principle, this study was appropriately designed to demonstrate efficacy in patients with predominantly negative symptoms.

Efficacy data and additional analyses

The short-term efficacy in acute exacerbation of schizophrenia has been shown as improvement primarily in PANSS total score supported by CGI-S scores for the dose range of 1.5-6 mg/day. Even though statistically significant difference for cariprazine has been shown over placebo with respect to reduction in PANSS total scores in the short term studies, in the responder analyses mainly the higher doses of 6 mg or 6-9 mg cariprazine were superior to placebo except in study RGH-MD-16 in which all dose groups showed statistically significant responder rates over placebo including the lowest 1.5 mg cariprazine.

However, applicant is not proposing to include higher than 6 mg/day doses due to tolerability issues, which is agreed by the CHMP. Therefore the results for the doses > 6 mg/day are seen only as supportive.

Even though statistically significant changes in CGI-S compared to placebo in all these three short-term studies with similar design were seen, numerical difference compared to placebo in these studies appeared to be quite modest as the mean change was less than 1 point. Also, the difference between placebo and cariprazine in CGI-I was 0.8 (range 0.5-0.8) at its maximum. Numerically results in CGI-S and CGI-I were not very convincing.

The more conservative analyses asked for has been performed and were consistent with the primary analyses with somewhat lower treatment effects. The results of the additional sensitivity analyses (BOCF, pMI) in PANSS score and CGI-S score in the studies RGH-MD-16 and RGH-MD-04 are rather consistent with the primary analysis and lead to reasonably similar estimates of the treatment effect. As well, non responder imputation and original LOCF imputation for PANSS response rates gave similar odds ratios and p-values. Further, CGI-S response rates, using non responder imputation, suggest that cariprazine has clinically relevant efficacy in the treatment of schizophrenia. In conclusion, considering the totality of the data, it is agreed that there is a relevant clinical efficacy for cariprazine, although modest, in the treatment of schizophrenia patients.

For the study RGH-MD-16 a statistically significant decrease in PANSS total score from baseline was seen in all the treatments groups compared to placebo. The LSMD for 1.5 mg/day cariprazine was -8.0 ($p = 0.0017$); for 3 mg/day, -8.2 ($p = 0.0013$); for 4.5 mg/day -10.5 ($p < 0.0001$) and for risperidone -16.0 ($p<0.0001$) (MMRM analysis). The PANSS responder status (≥30% decrease) was achieved in all cariprazine dose groups and risperidone treated patients with 31% ($p=0.015$), 36% ($p=0.002$), 36% ($p=0.001$) and 44% ($p<0.001$) in 1.5, 3, and 4.5 mg/day cariprazine and risperidone, respectively. The secondary end-point, CGI-S, also showed statistical significance over placebo in 3 mg and 4.5 mg/day dose groups but not for the lowest dose, 1.5 mg/day (MMRM) but the numerical difference appeared to be quite modest (0.4 ($p=0.0040$), -0.5 ($p=0.0003$), -0.6 ($p<0.0001$) and -0.8 ($p<0.0001$) points in cariprazine 1.5 mg/day, cariprazine 3 mg/day, cariprazine 4.5 mg/day and risperidone 4 mg/day, respectively). When the OC analysis was performed, none of the cariprazine dose groups showed a statistical significance over placebo in improvement of PANSS or CGI-S score. This is likely caused by the large number of patients discontinuing due to insufficient therapeutic effect in the placebo group. However, for the risperidone group the change in PANSS and CGI-S score was significantly higher compared to placebo with all sensitivity analysis. Moreover, in the risperidone treatment group a greater numeric difference was seen for both the primary and secondary parameters over cariprazine. For each of the treatment groups, a significant improvement relative to placebo was seen for all the additional efficacy parameters but the risperidone treatment group showed a numerical greater difference than the cariprazine treatment group. The short-term duration of the study, the acute treatment setting, and the study population, is not considered appropriate to evaluate negative symptoms, thus NSA-16 results could only be informative.

Anti-parkinsonian drugs were more frequently used in the cariprazine 4.5 mg/day group (25%) and the risperidone group (29%) compared to cariprazine 1.5 mg/day (19%). Since EPS scale was performed before administration, these side effects would have been more common in these groups. Both the anti-parkinsonian drugs and EPS could mask an improvement in negative symptoms as well as a positive outcome on cognitive impairment. The applicant has discussed the issue and agrees that EPS can mimic negative symptoms and that it is theoretically possible that this could influence the result. The study design would however address this issue since the efficacy analyses used a change from baseline to end, where at baseline there would not yet be any EPS due to pre-enrollment antipsychotic treatment as patients had a wash out period from previous antipsychotic medication during screening and at the end

there would not be any treatment emergent EPS as patients were already treated with anti-EPS, the analyses would not be affected by EPS or anti-EPS medication. The reasoning is acceptable.

In the study RGH-MD-04, statistically significant reductions in total PANSS were observed with cariprazine 6 mg/day (LSMD -8.8, p<0.0001) and 3 mg/day (LSMD -6.0, p=0.0044) and with the active-control aripiprazole 10 mg (LSMD -7.0 , p=0.0008) (MMRM, confirmed with LOCF analysis). On the other hand, the responder rates (PANSS≥30%) differed from placebo only for the 6 mg/day cariprazine and for the aripiprazole group (for 20% for placebo, 25% for 3 mg/day (p=0.28), 32% for 6 mg/day (p=0.027) and 30% for aripiprazole (p=0.0313). The results for the secondary end-point CGI-S were statistically significant for all the treatment groups both with MMRM and LOCF analysis although the numerical difference was less than 1 point: -0.4 .(p=0.0044), -0.5 (p<0.0001) and -0.4 (p<0.0001) points in cariprazine 3 mg/day, cariprazine 6 mg/day and aripiprazole 10 mg/day, respectively. Also the PMM sensitivity analysis showed consistency with the primary results. The improvements observed in the cariprazine groups and the aripiprazole treated patients were similar. The greatest mean NSA-16 total score was found in the placebo group. However, the study is considered too short to be appropriate to evaluate negative symptoms. In addition, the study population was not specific to evaluate negative symptoms since acute patients with positive symptoms were included and an improvement in that sub score is considered being a confounding factor as well as, depression, EPS and other factors. The study would not be appropriate to evaluate cognitive symptoms either.

Both primary and secondary efficacy parameters in the study RGH-MD-05 showed a statistically significant improvement from baseline to week 6. The LSMD compared to placebo was -9.9 (p<0.0001) for 6 to 9 mg/day group, -6.8 (p=0.0029) for 3 to 6 mg/day group for the PANSS total score (MMRM, confirmed with LOCF analysis). The responder rates (PANSS≥30%) did not differ from placebo for any of the dose groups (placebo (25%), 3-6 mg (29%, p=0.485), 6-9 mg (35%, p=0.07)). The secondary endpoint, change in the CGI-S was statistically significant in both dose groups compared to placebo even though the numerical difference was less than 1 point; -0.3 (p=0.0116) and -0.5 (p=0.0003) points in cariprazine 3-6 mg/day, cariprazine 6-9 mg/day, respectively. It should be noted that dose > 6 mg cariprazine is out of scope. Improvements in PANSS positive and PANSS negative subscale scores, CGI-I score, and NSA-16 total score, were also observed. However, as stated above, the study design, with regard to duration, setting, and patient population is not considered appropriate to evaluate the effect on negative and cognitive symptoms.

The maintenance of effect has been shown with relapse-prevention in the study RGH-MD-06. Only about 17% of the patients completed the entire study period. However, since the study was to be terminated when the last patient had been followed for 26 weeks, many of the discontinuations were according to protocol. In the primary analysis 52 placebo patients and 76 cariprazine patients were censored. Since fewer cariprazine patients had an event, more patients were censored due to study end. The applicant was requested to present the number of censored by reason for censoring by treatment group. A post hoc sensitivity analysis was performed using reference-based controlled imputation. This analysis was consistent with the primary analysis. The flexible dose, 3-9 mg cariprazine treatment, led to a decreased risk of relapse (25% versus 48%, p=0.001, hazard ratio [95% CI]; 0.45 [0.28, 0.73]). The 25th percentile for time to relapse was 92 days in the placebo group and 224 days in the cariprazine group (p=0.001). Dose range of 1.5 – 6 mg/day cariprazine is proposed in maintenance treatment. In a post hoc analysis without 9 mg cariprazine dose, time to relapse was longer and risk for relapse measured with hazard ratio (HR 0.40; 95% CI: 0.20 - 0.82) was significantly smaller in cariprazine than in placebo group. However, formally efficacy of cariprazine 1.5 mg/day dose for maintenance has not been studied. During the double-blind treatment phase no improvement in PANSS scores were seen. The same pattern was also observed for the other additional efficacy parameters. Regarding the negative symptoms rating, the design of the study is not appropriate for evaluating an improvement in negative symptoms. Since

other required additional measures of potentially confounding symptoms/diagnoses have not been taken into account, the potential improvement in negative symptoms should be assessed with caution.

Cariprazine's effects on negative symptoms were evaluated in the study RGH-188-005. The dose range of 3-6 mg/day cariprazine was reported to show a statistically significant improvement in PANSS negative factor score from the baseline in favour of cariprazine over risperidone from week 14 and onwards. The LS mean change for the decrease in PANSS negative factor score from baseline to week 26 was -8.9 and -7.4 for cariprazine and risperidone, respectively. Concerning the comparison of treatment groups the pairwise difference was -1.5 (95% CI: -2.4, -0.5, p= 0.002). The responder analysis on this primary efficacy variable with 20% cut-off for change reached statistical significance (69.2% in the cariprazine group and 58.1% in the risperidone group, difference between groups 11%). No data exists to evaluate what is considered a significant difference in negative symptom trials, therefore it is hard to interpret the clinical relevance of the study results. In this study, none of the estimated mean differences reached the significant difference -2.25 that had been used in the sample size calculation. However, statistically significant results were achieved also with a lower difference.

The secondary efficacy parameter was the change from baseline to week 26 in the PSP score analysed with MMRM and the LSMD for cariprazine was 14.3 and for risperidone was 9.7 ($p<0.001$). According to the literature (Nasrallah, 2008), between-group minimally important clinical difference (active treatment versus placebo) for the PSP is a 10-point category improvement, if the mean change in the PSP is also statistically significant. In this study between treatment groups the difference was always less than 5 points, however cariprazine was compared to an active comparator.

In summary both treatments have shown efficacy in improvement of negative symptoms in study RGH-188-005. Applicant argued that the observed effect size in study RGH-188-005 is larger than what has been claimed to be clinically relevant in other studies of antipsychotic treatments and hence can be regarded as clinically relevant also in this trial and continues that the clinical relevance of the statistically significant 4.6 point difference on the PSP is best explained by the very strong face validity of this scale and by the fact that improved patient functioning is a fundamental demonstration of the clinical significance of an effect, since restored patient functioning is a critical component of recovery. Improvement in PANSS factor score for negative symptoms and the corresponding improvement in PSP score are relevant for the overall conclusion on clinical efficacy supported by the improvements in the CGI-S and the CGI-I scores.

In order to evaluate negative symptoms in isolation from changes in other symptoms possible confounding factors should be stable. The change from baseline in PANSS total score, PANSS positive subscale and the PANSS general psychopathology score for both the treatment groups were similar and not statistically significant. The change in PANSS positive subscale score was small which is important since an improvement in positive symptoms might have an effect on negative symptom and hence confound the results. Although not statistically significant, the change from baseline in PANSS general psychopathology score (that contains 2 items from the primary endpoint measure – i.e. PANSS items G7 and G16) in the cariprazine and the risperidone treatment groups was -7.14 and -6.42 respectively which is considered numerically large enough to have an influence on the overall assessment of negative symptoms. The PANSS positive factor score and CDDS were consistent through the study and hence are not considered having influenced the rating of negative symptoms.

A total of 157 cariprazine treated patients (69.2%) achieved decreases of at least 20% in PANSS factor score for negative symptoms compared to 133 risperidone treated patients (58.1%) ($p=0.002$). Although there is a statistically significant difference between the two groups and the results suggest an effect on negative symptoms, there is no adequate consensus regarding when an improvement in negative symptoms is clinically relevant. The relevance of a 20% decrease has been further justified. The applicant states that the clinical relevance of the chosen responder definition is based on schizophrenia literature

stating that a 20-25% responder rate is considered clinically relevant in treatment resistant illnesses (Leucht, 2005) and that 20% improvement on the PANSS-FSNS would be considered a valid response (Edgar, 2014).The responder rates achieving ≥ 20 % improvement were higher in the cariprazine treatment group (69.2%) than in the risperidone treatment group (58.1%). The analysis imputing non-responders for missing values was also in favor of cariprazine treatment group (61.7% versus 52.8%).

Responder analysis using 30% cut-off was performed as requested. The responder rates achieving ≥ 30% improvement were again higher in the cariprazine treatment group (49.8%) than in the risperidone treatment group (36.2%) (p=0.003). The analysis imputing non-responders for missing values was in favour of cariprazine treatment group (45.4 versus 33.6%).To conclude, there would be individuals that would improve on cariprazine and there would also be some improving on risperidone concerning both positive and negative symptoms.

Analyses of the primary efficacy endpoint for the ITT population were performed with key baseline characteristics as covariates. Some of the key variables were: countries of recruitment, baseline PANSS factor score for negative symptom, baseline PANSS items, conceptual disorganization (P2), excitement (P4), hostility (P7), anxiety (G2), depression (G6), and baseline PSP and CDSS scores. No treatment-by-characteristic interaction term was significant at the 5% level. Although exploratory, the covariate analysis was found to be informative for the robustness of the primary endpoint. The Applicant was also asked to analyse whether the improvements in other factor scores, cognitive (P2, N5, G11), depression/anxiety (G2, G3, G6), and excitement (P4, P7, G8, G14) have influenced the improvement of negative factor score. This analysis showed statistical superiority of cariprazine over risperidone.

The Applicant has provided discussion for the need for a separate indication in the treatment of negative symptoms. However, the CHMP concluded that although an effect on negative symptoms has been shown, the indication "schizophrenia in adults" already covers both positive and negative symptoms and therefore addition of the second line as a separate patient population is not necessary. The effects on cariprazine on negative symptoms are described in sufficient detail in SmPC section 5.1.

2.6.4. Conclusions on the clinical efficacy

In the short-term studies, even though robust statistical significance was reached in both primary and secondary endpoints, the efficacy is illustrated by numerically modest improvement in primary and secondary endpoints, depending on the study and dose. Improvement was higher with active comparator risperidone and similar with aripirazole when used with minimal effective dose. Efficacy in long-term use was confirmed in the randomised withdrawal study.

The effect of cariprazine on negative symptoms was statistically superior to risperidone in the dedicated study of patients with predominantly negative symptoms. However, the clinical relevance of the difference is difficult to interpret.

2.7. Clinical safety

Patient exposure

The clinical development program of cariprazine included 42 studies; 13 PK / PD studies, 18 Phase 2/3 clinical studies and 11 additional Japanese studies of which 37 studies are completed (*i.e.*, database lock by 5 Oct 2015), and 5 are ongoing.

A total of 9344 healthy subjects and patients with various mental disorders have been included in the cariprazine studies, and 6120 of them received at least 1 dose of cariprazine.

Table 34. Number of subjects who received investigational product (*i.e.*, placebo / cariprazine / risperidone / aripiprazole) during the cariprazine clinical development program. The 8 studies, which form the basis for primary safety assessment in the schizophrenia indication are shaded in grey.

Study	***Placebo***	***Cariprazine***	***Risperidone***	***Aripiprazole***	***Total[a]***
Phase 2/3 Studies in Schizophrenia					
Placebo-controlled total (Group 1A)	584	1317	140	152	2193
Placebo-controlled, fixed-dose	304	750	140	152	1346
Placebo-controlled, flexible-dose	280[a]	567[a]	—	—	847
Uncontrolled, long-term (Group 1B)	—	679 [416][b]	—	—	679 [235][c]
RGH-MD-06	99	765	—	—	765[d]
RGH-188-005	—	230	230	—	460
Phase 2/3 Studies in Schizophrenia Subtotal	***683***	***2728[b]***	***370***	***152***	***3653[c]***
Phase 2/3 Studies in Other Indications					
Bipolar mania placebo-controlled total	442[a]	623[a]	—	—	1065
Bipolar mania uncontrolled, long-term	—	402 [all new]	—	—	402
Mania studies Subtotal	***442***	***1025***	**—**	**—**	***1467***
Bipolar depression placebo-controlled	222[e]	583	**—**	**—**	805
Bipolar depression uncontrolled, long-term	**—**	**—**	**—**	**—**	**—**
Bipolar depression studies Subtotal	***222***	***583***	**—**	**—**	***805***
MDD placebo-controlled total	347	695	—	—	1042
MDD uncontrolled, long-term	**—**	**—**	**—**	**—**	**—**
MDD studies Subtotal	***347***	***695***	**—**	**—**	***1042***
Clinical PK and PK/PD Studies					
Healthy subjects (Group 3A)	23	241	—	—	***253[f]***
Patients with schizophrenia (Group 3B)	91[g]	153[h]	—	—	***244***
Japanese Studies					
Completed Japanese studies	12	240	—	—	***252***
Ongoing Japanese studies [i]	DB	DB	DB	—	***748***
Ongoing studies [i]					
RGH-MD-72	DB	DB	—	—	***425***
RGH-MD-76	—	345	—	—	***345***
RGH-188-101	—	110	—	—	***110***
GRAND TOTAL	**1820**	**6120**	**370**	**152**	**9344**

a = GCP violation sites are also included, therefore safety population of ISS different from safety population of CSRs, where GCP violation sites were excluded

b = In Study RGH-MD-11, 416 patients were randomized newly to cariprazine, who were either newly enrolled (235) or received placebo or active comparator in the lead-in study. For the total of patients receiving cariprazine 416 patients were counted (Appendix 120-SUR, Table 1.1.5)

c = For the total of patients involved in cariprazine clinical studies, only the newly enrolled (235) patients were counted for Group 1B
d = In Study RGH-MD-06 all patients received cariprazine in the run-in phase, later 99 patients were switched to placebo.
e = One patient in the placebo group who has been randomized twice is only counted once.
f = 11 patients in Group 3A received both placebo and cariprazine in a cross-over design study and are counted only once in the total column
g = Placebo group includes patient on placebo/risperidone/moxifloxacin also
h = 4 patients in the cariprazine group were allocated to cariprazine, however prematurely discontinued study before actually receiving cariprazine. Since safety population for the study was defined by allocation and not by treatment, they were counted to cariprazine
i = For ongoing studies, patient numbers are as of 5 Oct 2015. For blinded data numbers are taken from DSUR 2015.
Note: Totals are tallied by row. PD = pharmacodynamic; PK = pharmacokinetic.
Source: Appendix 120-SUR, Table 1.1.5; Appendix NDA, Table 1.1.3; individual study reports, Module 5.

In the Phase 2/3 schizophrenia studies 2728 patients were treated with cariprazine. Safety data was analysed according to modal daily doses grouped into 3 dose subgroups (cariprazine modal daily dose of 1.5-3 mg/day, 4.5-6 mg/day and 9-12 mg/day). Based on study design, dosage, and patient populations, the clinical studies in schizophrenia have been categorized into distinct groups:

- **Group 1A** (1317 patients), pooled data from 6-week, controlled schizophrenia studies, RGH-MD-03, RGH-MD-04, RGH-MD-05, RGH-MD-16 performed with cariprazine dose range 1.5 to 12 mg/day and active controls risperidone 4 mg/day and aripiprazole 10 mg/day,
- **Group 1B** (679 patients), pooled data from 48 week open-label safety studies, RGH-MD-11 and RGH-MD-17, performed with 1.5 to 9 mg/day cariprazine,
- **RGH-MD-06** (765 patients), maintenance of effect study with 3 to 9 mg/day cariprazine,
- **RGH-188-005** (230 patients), negative symptom study with 3 to 6 mg/day cariprazine and active control risperidone 4 mg/day.

Cariprazine in the dose range targeted for the treatment of schizophrenia (1.5-6mg/day) has also been investigated in other patient populations (such as bipolar mania 3-12 mg, bipolar depression (BD) 0.25-3 mg and major depressive disorder (MDD) 0.1-4.5 mg). Short-term, mania studies (RGH-MD-31, RGH-MD-32, and RGH-MD-33) have been grouped to **Group 2A**, the long-term mania study (RGH-MD-36) has been labelled **Group 2B**. Data from the two short-term bipolar depression studies (RGH-MD-52, RGH-MD-56) have been pooled and so were data from the two completed short-term major depressive disorder studies (RGH-MD-71, RGH-MD-75). PK/PD data from healthy volunteer studies (RGH-188-001, RGH-188-002, RGH-188-003, RGH-PK-04, RGH-PK-07, RGH-PK-10, RGH-PK-14) were grouped to **Group 3A**. PK/PD data from schizophrenic patients from studies RGH-MD-01, RGH-MD-02, RGH-MD-14, RGH-MD-18 and RGH-PK-15 were grouped to **Group 3B**.

More than 960 patients with schizophrenia have been exposed to cariprazine for at least 12 weeks, ~600 patients for at least 24 weeks and ~270 patients for at least 48 weeks. For the claimed posology of 1,5-6 mg/day, 508 patients were exposed for 6 months and 225 for 12 months. Moreover, 122 cariprazine treated patients (from RGH-MD-06) in the claimed posology were exposed for more than 12 months. Size of the safety database at 6 and 12 months meets the requirements in the ICH E1 guidance (CPMP/ICH/375/95, ICH E1).

Table below lists the overall exposure to the drug in the schizophrenia program by treatment time.

Table 35. Extent of exposure to cariprazine in the Phase 2/3 schizophrenia studies.

Exposure	*All patients in schizophrenia phase 2/3 trials (N = 2991[a])*	*Group 1A*	*Group 1B*	*RGH-MD-06*	*RGH-188-005*
		Cariprazine (N = 1317)	**Cariprazine (N = 679)**	**Cariprazine (N = 765)**	**Cariprazine (N = 230)**

Treatment duration, n (%)[b]					
≥ 1 day	2991 (100.0)	1317	679	765	230
≥ 3 weeks	2421 (80.9)	994	592	615	214
≥ 6 weeks	1874 (62.7)	676	511	474	211
≥ 12 weeks	969 (32.4)	—	449	329	184[d]
≥ 24 weeks	614 (20.5)	—	346	90	178[d]
≥ 48 weeks	268 (9.0)	—	211	57	—
Patient-years exposure[c]	**795.4**	**117.9**	**350.3**	**229.6**	**97.6**

a = Roll-over patients from short-term studies into long-term safety extensions are counted only once in the total
b = Treatment duration for cariprazine-treated patients was calculated as the number of days from the date of first dose of cariprazine taken to the date of last dose of cariprazine taken (inclusive of the gap in dosing between lead-in and extension studies for patients who took cariprazine in both).
c = Patient-years = (total treatment duration in days)/365.25.
d = ≥ 14 weeks and ≥ 26 weeks for RGH-188-005
Source: Appendix NDA-R, VI, Table 2.1.1 and 2.1.3; Appendix EU-MAA, Tables 2.1.7, 2.6.1 and RGH-188-005, CSR, Table 14.1.1.1

Baseline demographic characteristics were similar for patients enrolled in the schizophrenia program and were generally representative for the targeted patient population.

Table 36. Baseline demographics and other patient characteristics in the clinical schizophrenia studies.

Patient Characteristic	***Group 1A***	***Group 1B***	***RGH-MD-06***		***RGH-188-005***
	Cariprazine (N = 1317)	**Cariprazine (N = 679)**	**Cariprazine Run-in-Phase (N = 765)**	**Cariprazine Double-Blind Safety (N = 101)**	**Cariprazine (N = 230)**
Age, mean ± SD, years	37.8 ± 10.4	38.5 ± 10.9	38.4 ± 10.4	39.2 ± 10.9	40.2 ± 10.5
Age, n (%)					
< 55 years	1232 (93.5)	623 (91.8)	723 (94.5)		86.1%
≥ 55 years	85 (6.5)	56 (8.2)	42 (5.5)		13.9%
Sex, n (%)					
Male	945 (71.8)	471 (69.4)	544 (71.1)		124 (53.9)
Female	372 (28.2)	208 (30.6)	221 (28.9)		106 (46.1)
Race, n (%)					
White	574 (43.6)	302 (44.5)	299 (39.1)	45 (44.6)	221 (96.1)
All other races	709 (53.8)	362 (53.3)	466 (60.9)	56 (55.4)	0
Black/African-American	440 (33.4)	240 (35.3)	303 (40.9)	31 (30.7)	0
Asian	232 (17.6)	98 (14.4)	149 (19.5)	25 (24.8)	0
Other	37 (2.8)	24 (3.5)	4 (0.5)	0	0
Mean BMI, kg/mP^2	26.07	26.81	26.5	26.39	27.03
Mean duration of disorder, years	12.5	12.2	12.9		12.0

Note: Percentages are rounded. Race data were not collected for patients enrolled at study centers in Romania in Study RGH-MD-04 and in France in Study RGH-188-005, per local regulations.
BMI = body mass index, SD=standard deviation. Duration of disorder = duration since first diagnosis of schizophrenia; Mean age at onset = mean age when first diagnosed with schizophrenia.
Source: Appendix NDA-R, VI, Tables 3.1.1, 3.1.2, 3.3.1, 3.3.2 ; RGH-MD-06, Tables 14.2.1A, 14.2.2A, 14.2.4A; RGH-188-005, Table 14.1.2.1, 14.1.3.1, 14.1.4.1.3.

Mean age was about 38 years; more patients (69%) were male than female; and about half (49.7%) of the patients were Caucasian. Patients of all other races were mostly Black/African American or Asian. Most patients were overweight, with a baseline mean BMI ⩾ 26 kg/m2. Most patients had schizophrenia of the paranoid type (according to DSM IV-TR). The mean duration of schizophrenia was approximately 12 years, with most patients first diagnosed with schizophrenia in their mid-20s. The percentage of male patients included in the studies was higher in Groups 1A, 1B and RGH-MD-06 than in RGH-188-005.

Adverse events

In the targeted dose range of 1.5-6 mg/day, the most frequent TEAEs (defined as occurring in more than 10% of patients) were akathisia (14.6%), insomnia (14.0%), and headache (12.1%). Other common AEs were restlessness (6.2 %), weight increased (5.1 %), dizziness (4.5 %), and creatine phosphokinase (CPK) increased (2.6 %). In the pooled schizophrenia dataset – within a wide dose-range 1.5–12.0 mg/day – a dose-dependency was seen for increased CPK and alanine aminotransferase (ALT) as well as hypertension. For the claimed posology of 1.5-6 mg/day, dose dependency was observed for TEAEs blurred vision, CPK elevation, akathisia/restlessness, insomnia and anxiety.

Table 37. AEs (⩾ 2 % in the cariprazine 1.5 – 6.0 mg group) in the pooled data set of schizophrenia studies. The most relevant dose range is shaded in grey.

Preferred term (PT)	*Placebo N=683 n (%)*	*Cariprazine 1.5–6 mg N=2048 n (%)*	*Cariprazine 9–12 mg N=741 n (%)*	*Cariprazine overall N=2728 n (%)*
Patients with at least one AE	**467 (68.4)**	**1569 (76.6)**	**610 (82.3)**	**2137 (78.3)**
Gastrointestinal disorders				
Nausea	31 (4.5)	141 (6.9)	40 (5.4)	181 (6.6)
Constipation	32 (4.7)	113 (5.5)	48 (6.5)	161 (5.9)
Dyspepsia	21 (3.1)	100 (4.9)	35 (4.7)	135 (4.9)
Vomiting	24 (3.5)	91 (4.4)	30 (4.0)	121 (4.4)
Diarrhoea	23 (3.4)	72 (3.5)	34 (4.6)	106 (3.9)
Toothache	22 (3.2)	61 (3.0)	33 (4.5)	94 (3.4)
Abdominal discomfort	16 (2.3)	41 (2.0)	24 (3.2)	65 (2.4)
Infections and infestations				
Nasopharyngitis	10 (1.5)	49 (2.4)	23 (3.1)	71 (2.6)
Investigations				
Weight increased	10 (1.5)	104 (5.1)	50 (6.7)	154 (5.6)
Blood creatine phosphokinase increased	11 (1.6)	54 (2.6)	33 (4.5)	87 (3.2)
Metabolism and nutrition disorders				
Decreased appetite	13 (1.9)	52 (2.5)	17 (2.3)	69 (2.5)
Musculoskeletal and connective tissue disorders				
Back pain	14 (2.0)	65 (3.2)	12 (1.6)	77 (2.8)
Pain in extremity	16 (2.3)	42 (2.1)	23 (3.1)	65 (2.4)
Nervous system disorders				
Akathisia	23 (3.4)	299 (14.6)	107 (14.4)	404 (14.8)
Headache	81 (11.9)	247 (12.1)	94 (12.7)	340 (12.5)
Extrapyramidal disorder	22 (3.2)	143 (7.0)	58 (7.8)	198 (7.3)
Tremor	11 (1.6)	112 (5.5)	33 (4.5)	142 (5.2)
Dizziness	15 (2.2)	92 (4.5)	34 (4.6)	125 (4.6)
Sedation	21 (3.1)	75 (3.7)	27 (3.6)	102 (3.7)

Somnolence	13 (1.9)	63 (3.1)	26 (3.5)	89 (3.3)
Psychiatric disorders				
Insomnia	69 (10.1)	287 (14.0)	94 (12.7)	379 (13.9)
Restlessness	20 (2.9)	126 (6.2)	53 (7.2)	178 (6.5)
Anxiety	27 (4.0)	141 (6.9)	32 (4.3)	172 (6.3)
Schizophrenia	60 (8.8)	101 (4.9)	41 (5.5)	142 (5.2)
Agitation	27 (4.0)	78 (3.8)	18 (2.4)	95 (3.5)
Psychotic disorder	19 (2.8)	44 (2.1)	22 (3.0)	66 (2.4)

N = number of patients in the safety population, n (%) = number and percentage of patients with specified event,
AE = adverse event
Source: Appendix EU-MAA, Table 5.1.10

The Applicant had identified AEs of special interest based on i) class effects of atypical antipsychotics, ii) findings from the non-clinical cariprazine program and iii) safety findings identified by the company or regulatory authorities. These AEs are listed in the Table below.

Table 38. AEs of special interest.

Adverse events of special interest
Suicidality
Class effects
EPS (dyskinesia, dystonia, parkinsonoid, akathisia, restlessness, tardive dyskinesia)
Seizures / convulsions
Neuroleptic malignant syndrome (NMS)
Deep vein thrombosis / Pulmonary embolism
Cognitive impairment and Delirium
Cerebrovascular disease
Sedation
Sexual dysfunction
Autonomic nervous system disorders (Orthostatic hypotension, enuresis, vasomotor rhinitis, temperature changes, hypersalivation, dry mouth)
Prolactine increase
Cardiovascular disease / sudden death / QT prolongation (causes ventricular arrhythmia, torsades de pointes)
Weight increase / metabolic syndrome
Haematopoetic changes (leucocytosis, leucopenia (agranulocytosis), eosinophilia)
Liver enzyme increase
Rhabdomyolysis (muscle pain, weakness, CPK increase, renal failure due to myoglobin set free from damaged muscle cells, myoglobulinuria)
Non-clinical findings
Ocular effects (cataract, retinal degeneration, atrophy)
Phospholipidosis / fibrosis
Body weight changes either way
ALT / AST elevations
Cholesterol / Triglyceride decreases
Reproductive toxicity
Findings identified by the company or regulatory authorities

Adverse events of special interest
Akathisia / EPS
Increase in blood pressure
Increase in CPK / rhabdomyolysis
ALT / AST elevations
Phospholipidosis

The overall incidence of TEAEs was highest for cariprazine claimed posology (76.6%) followed by placebo (68.4%), aripiprazole (65.8%) and risperidone (61.1%). However, pooled data provided includes studies of different design. In the clinical studies TEAEs were reported more frequently for cariprazine claimed posology than for active comparator(s) in SOCs Blood and lymphatic system disorders; Injury, poisoning and procedural complications; Investigations; Metabolism and nutrition disorders; Musculoskeletal and connective tissue disorders; Nervous system disorders; Psychiatric disorders.

The AEs observed among cariprazine-treated patients were generally consistent with currently approved atypical antipsychotics. The most frequent TEAEs (defined as ≥ 5% of cariprazine-treated patients and at least twice the rate for placebo in the placebo-controlled studies, as ≥ 10% of patients in the open-label studies and as ≥ 5% in the negative symptoms study) for the respective groups are presented in Table 5.2-2.

Table 5.2-2 **Summary and Incidence of Most Frequent Treatment-Emergent Adverse Events in the Schizophrenia Program — Safety Population**

Preferred Term	*Schizophrenia*						
	Group 1A		*Group 1B*	*RGH-MD-06*			*RGH-188-005*
	Placebo (N = 584)	Cariprazine (N = 1317)	Cariprazine (N = 679)	Cariprazine (N=765)	Placebo (N = 99)	Cariprazine (N = 101)	Cariprazine (N = 230)
Akathisia	21 (3.6)	149 (11.3)	105 (15.5)	147 (19.2)	3 (3.0)	5 (5.0)	19 (8.3)
Extrapyramidal disorder	20 (3.4)	100 (7.6)	45 (6.6)	56 (7.3)	3 (3.0)	6 (5.9)	4 (1.7)
Restlessness	18 (3.1)	65 (4.9)	38 (5.6)	71 (9.3)	2 (2.0)	2 (2.0)	5 (2.2)
Tremor	11 (1.9)	55 (4.2)	47 (6.9)	38 (5.0)	0	8 (7.9)	4 (1.7)
Headache	74 (12.7)	147 (11.2)	87 (12.8)	92 (12.0)	7 (7.1)	7 (6.9)	13 (5.7)
Insomnia	63 (10.8)	160 (12.1)	90 (13.3)	110 (14.4)	8 (8.1)	8 (7.9)	21 (9.1)
Weight increased	8 (1.4)	37 (2.8)	71 (10.5)	44 (5.8)	3 (3.0)	4 (4.0)	1 (0.4)
Schizophrenia	47 (8.0)	54 (4.1)	39 (5.7)	26 (3.4)	13 (13.1)	8 (7.9)	15 (6.5)
Anxiety	24 (4.1)	64 (4.9)	58 (8.5)	38 (5.0)	3 (3.0)	4 (4.0)	13 (5.7)
Somnolence	13 (2.2)	34 (2.6)	26 (3.8)	21 (2.7)	0	3 (3.0)	9 (3.9)
Back pain	12 (2.1)	36 (2.7)	21 (3.1)	17(2.2)	2 (2.0)	5 (5.0)	0

Note: Most frequent TEAEs are those reported for ≥ 5% of patients in the cariprazine group and at a rate ≥ 2 times that of the placebo group during the double-blind treatment period in the controlled schizophrenia studies, for ≥ 10% of patients in the open-label studies and for ≥ 5% in the negative symptoms study. % = percentage of patients with the adverse event; TEAE = treatment-emergent adverse event.

Extrapyramidal symptoms / akathisia

Extrapyramidal symptoms, primarily akathisia, were among the most frequent TEAEs in the cariprazine development program (akathisia 15%, extrapyramidal disorder 7.3% in the overall cariprazine groups).

Other EPS included restlessness, dystonia cluster, parkinsonism cluster, musculoskeletal stiffness and tardive dyskinesia.

In Group 1B studies, the frequency of patients experienced parkinsonism cluster were higher than that observed in Group 1A studies (18% in Group 1B and 5% in Group 1A) as expected due to the longer duration of these studies.

In the maintenance of effect study (RGH-MD-06), the incidence of all EPS-related TEAEs reported during the 20 week open-label phase were higher than during the double-blind treatment period (40% in open-label phase, 21% in cariprazine 3-9 mg during double-blind phase, 7% in placebo), while akathisia was reported in 19% during open-label and 5% during double-blind phase in cariprazine group and in 3% of placebo. There were 2 EPS-related SAEs during the open-label phase while no EPS-related SAEs were observed during the double-blind treatment period.

During the double-blind treatment period of the negative symptoms study (RGH-188-005) the percentage of patients with all EPS-related TEAEs were 14.3% in cariprazine and 13% in risperidone groups. Akathisia was reported in 8.3% in cariprazine and 5.2% in risperidone group. No EPS-related SAE was reported in any group.

Most cases of akathisia and EPS were reported for the first time within the first 6 weeks of treatment. However, in long-term studies in a few cases of later onset of first akathisia were observed up to 36 weeks.

Dose dependency was seen for akathisia with overall frequencies in corresponding cariprazine dose groups; 1.5 mg: 7.8%, 3 mg: 15.7%, 4.5 mg: 9.1%, 6 mg: 18.0%, but not for the other types for EPS.

Blood pressure and pulse rate elevations

Elevations in blood pressure and increases in pulse rate were reported with cariprazine treatment in the claimed posology (Table 27).

Regarding treatment emergent adverse events, more patients experienced hypertension related TEAEs in the cariprazine claimed posology group than in the other groups (cariprazine 2.6%; risperidone 1.6%, aripiprazole 0.7%, Table 100.2). In the schizophrenia studies, no dose dependency was seen for the preferred terms of hypertension (1.5mg: 2.2%, 3mg: 1.6%, 4.5mg: 1.5%, 6mg: 1.9%), blood pressure increased (1.5mg: 0%, 3mg: 1.1%, 4.5mg: 0.2%, 6mg: 1.0%), heart rate increased (1.5mg: 0.6%, 3mg: 0.6%, 4.5mg: 0.4%, 6mg: 0.8%) or tachycardia (1.5mg: 0.6%, 3mg: 1.6%, 4.5mg: 1.1%, 6mg: 1.1%). However, for grouped TEAEs, dose dependency was seen for increased and decreased heart rate.

Most hypertension grouped TEAEs were considered by the Investigators as mild or moderate in intensity. Hypertension was mostly controlled with antihypertensive medication (53.7% of the patients with TEAE in the cariprazine claimed posology group, 28.6% in the placebo group and 0% for comparators, Table 100.3). Three patients (0.1%) in the cariprazine claimed posology group discontinued the study due to hypertension and none had their study drug down-titrated due to this AE. For most cases no intervention was taken.

Table 39. Change from Baseline to End in Vital Signs – Safety population

	Placebo	*Cariprazine Modal Daily Dose*				*Claimed posology*	*Risperidone*	*Aripiprazole*
		1.5 mg	*3 mg*	*4.5 mg*	*6 mg*			
Group 1A								
Mean systolic BP change ± SD	0.9±10.4	0.4±10.1	0.7±9.6	0.7±12.4	1.9±9.8	1.0±10.4	-2.2±10.1	1.7±8.9
Mean diastolic BP change ± SD	0.4±8.0	0.2±7.0	0.1±7.9	2.1±8.7	1.3±8.0	0.9±8.0	-1.6±7.7	0.8±7.4
Mean change in pulse rate ± SD	-0.1±12.6	0.0±10.6	-0.2±11.3	1.3±12.4	1.0±11.3	0.5±11.5	0.2±12.8	0.0±11.7
Group 1B								
Mean systolic BP change ± SD		0.0±7.6	0.6±11.9	0.8±11.5	1.1±11.0	0.9±11.2		
Mean diastolic BP change ± SD		-0.5±9.4	1.0±8.6	0.3±7.8	-0.0±8.6	0.3±8.5		
Mean change in pulse rate ± SD		0.5±16.6	-2.2±12.1	0.3±11.3	-2.1±12.2	-1.8±12.2		
RGH-MD-06 OL								
Mean systolic BP change ± SD			1.3±11.6		1.4±10.8	1.4±11.2		
Mean diastolic BP change ± SD			0.5±8.3		0.7±8.7	0.6±8.5		
Mean change in pulse rate ± SD			0.3±10.3		-0.2±11.6	–0.1±11.0		

	Placebo	*Cariprazine Modal Daily Dose*				*Claimed posology*	*Risperidone*	*Aripiprazole*
		1.5 mg	*3 mg*	*4.5 mg*	*6 mg*			
RGH-MD-06 DB								
Mean systolic BP change ± SD	-0.3±12.0		-3.1±12.4		1.4±14.9	0.2±13.7		
Mean diastolic BP change ± SD	-0.7±9.3		-1.4±5.9		0.7±9.7	0.1±7.8		
Mean change in pulse rate ± SD	-2.3±13.4		-5.8±10.6		-1.1±10.8	–2.4±10.7		
RGH-188-005								
Mean systolic BP change ± SD				–0.6±9.57		–0.6±9.57	–0.3±9.84	
Mean diastolic BP change ± SD				–0.8±8.59		–0.8±8.59	–0.0±7.78	
Mean change in pulse rate ± SD				–0.8±10.69		–0.8±10.69	0.9±10.45	

Blood Creatinine Phosphokinase Elevations and Muscle Injury

Elevations of creatinine phosphokinase (CPK) were dose-dependent. Overall, TEAEs reported with frequency of 2.6% in 1.5-6 mg cariprazine groups and.6% in placebo. Potentially clinically significant changes in CPK levels and incidence of CPK related TEAEs in the schizophrenia studies are summarized in Table below.

Table 40. Potentially Clinically Significant Changes in CPK levels and Incidence of CPK Related TEAEs in the Schizophrenia Studies – Safety Population

Group	*CPK > 1.5 × ULN*	*CPK > 1000 U/L*	*CPK > 5000 U/L*	*CPK Related TEAEs*
Group 1A				
Placebo	66/465 (14.2)	19/550 (3.5)	0/555 (0)	8/584 (1.4)
Cariprazine1.5-6mg	195/899 (21.6)	47/1027 (4.6)	3/1037 (0.3)	21/1114 (1.9)
Risperidone 4 mg	26/113 (23.0)	6/132 (4.5)	0/133 (0)	5/140 (3.6)
Aripiprazole 10mg	24/127 (18.9)	3/147 (2.0)	1/147 (0.7)	3/152 (2.0)
Group 1B				
Cariprazine1.5-6mg	151/444 (34.0)	45/517 (8.7)	6/517 (1.2)	26/531 (4.9)
RGH-MD-06 OL				
Cariprazine 3-6mg	37/151 (24.5)	7/174 (4.0)	0/176 (0.0)	7/337 (2.0)
RGH-MD-06 DB				
Placebo	23/88 (26.1)	1/95 (1.1)	0/97 (0.0)	3/99 (3.0)
Cariprazine 3-6mg	9/38 (23.7)	2/51 (3.9)	0/51 (0.0)	1/51 (1.9)
RGH-188-005				
Cariprazine 4.5mg	9/203 (4.4)	3/203 (1.5)	0/203 (0)	3/230 (1.3)
Risperidone 4 mg	2/195 (1.0)	3/195 (1.5)	0/195 (0)	2/230 (0.9)

Elevations in liver enzymes

Increases were observed for liver aminotransferases with no cariprazine-induced serious liver injury. TEAEs related to increases in aminotransferases are presented in Table below.

Table 117.2 Incidence of Specific Treatment Emergent Adverse Events Associated with Hepatic Enzyme Increase During Treatment Period, Cariprazine Schizophrenia Program, Safety Population

Preferred Term	PL (N=683) n(%)	Cariprazine 1.5 mg (N=180) n(%)	Cariprazine 3.0 mg (N=619) n(%)	Cariprazine 4.5 mg (N=549) n(%)	Cariprazine 6.0 mg (N=794) n(%)	CAR 1.5-6.0 mg (N=2048) n(%)	Risperidone (N=370) n(%)	Aripiprazole (N=152) n(%)
Patients with at least one Grouped TEAE	**3 (0.4)**	**4 (2.2)**	**13 (2.1)**	**4 (0.7)**	**25 (3.1)**	**46 (2.2)**	**6 (1.6)**	**0**
Alanine aminotransferase increased	2 (0.3)	3 (1.7)	8 (1.3)	4 (0.7)	20 (2.5)	35 (1.7)	5 (1.4)	0
Aspartate aminotransferase increased	2 (0.3)	2 (1.1)	5 (0.8)	2 (0.4)	13 (1.6)	22 (1.1)	2 (0.5)	0
Hepatic enzyme increased	0	0	4 (0.6)	0	2 (0.3)	6 (0.3)	1 (0.3)	0
Alanine aminotransferase abnormal	0	0	1 (0.2)	0	0	1 (0.0)	0	0
Transaminases increased	0	0	0	0	1 (0.1)	1 (0.0)	0	0

Source: Appendix EU-120 Table 117.1

Table below lists the incidence of TEAEs related to hepatic injuries.

Table 117.3 Incidence of Hepatic Laboratory Parameter and Hepatic disease related ADRs from pooled schizophrenia ADR table, Cariprazine Schizophrenia Program, Safety population

Preferred term	Placebo (N=683) n (%)	Cariprazine (N=2048) 1,5-6 mg n(%)	Risperidone N=370 n(%)	Aripiprazole N=152 n(%)
Hepatitis	1 (0.1)	1 (0.0)	0	0
Hepatitis toxic	0	1 (0.0)	0	0
Hyperbilirubinaemia	0	2 (0.1)	1 (0.3)	0

Source: Appendix EU-120, Table 5.1.10A

Ocular effects

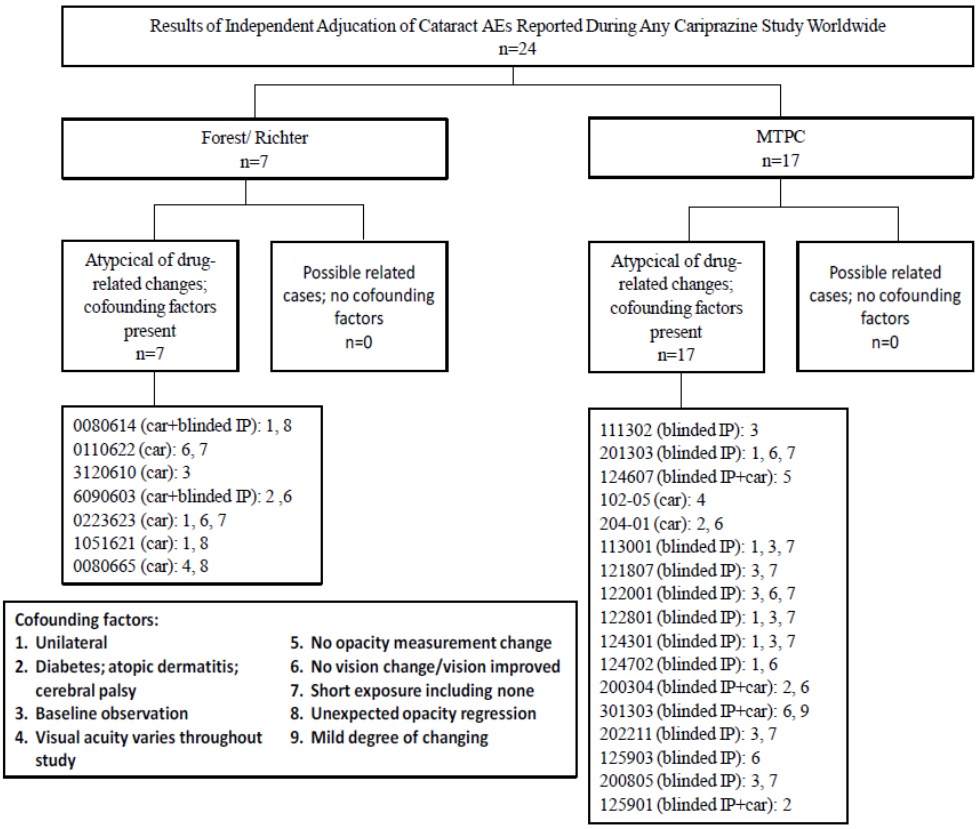
Bilateral cataract and cystic degeneration of the retina were observed in the nonclinical program. Ophthalmologic monitoring, including best-corrected visual acuity (BCVA), IOP, slit-lamp, and LOCS III, was implemented in the cariprazine long-term studies of Group 1B (RGH-MD-17 and RGH-MD-11), the maintenance of efficacy study (RGH-MD-06), the negative symptoms study (RGH-188-005) and the long-term mania study (Group 2B, RGH-MD-36). Because the long-term studies in Group 1B included roll-over patients from the short-term schizophrenia studies, ophthalmologic monitoring was implemented at baseline and at endpoint (Week 6) in studies RGH-MD-04 and RGH-MD-05.

Ocular adverse events

The most commonly reported ocular AE was blurred vision, for which there was an apparent dose-response relationship with cariprazine. Two patients had an AE of cataract. Six patients (0.3%) discontinued treatment due to ocular AEs: 2 cases of cataract, and eye disorder, eye swelling, ocular hyperemia, optic neuropathy, and visual acuity reduced.

Overall, there have been 6 cataract cases reported in the schizophrenia program, 1 in the mania development program and 17 in Japanese schizophrenia studies. These numbers include cataract cases observed outside the claimed posology. In the schizophrenia claimed posology group there were 3 cases of cataracts reported. For some of the cases the Applicant was able to gather further information to better understand the nature and relevance of these reported cases and reanalyzed them with the new information, where applicable. All of the 14 related cataracts were claimed to have clinical confounding factors as outlined in the Figure below.

Figure 2.1.5.12-1 Summary of Adverse Events Related to Cataract



Six cases were reported in the schizophrenia development program, out of which one was a baseline case (#3). Out of the remaining 5 cases, case#2 occurred after 28 days of cariprazine treatment. Case#5 occurred in a patient who had been diagnosed with diabetes mellitus, and previously had taken chrorpromazine which is proven to be cataractogenic. Case#6 had corresponding risk due to the age of the patient. The other two cases (#1 and #4) of cataract resolved after discontinuation. Although it is questionable for a cataract to resolve over time due to its pathophysiology, drug induced adverse reactions, in general, tend to disappear after discontinuation. From these two resolved cataract cases, case#4 occurred in a 58 years-old patient who concomitantly took statin (atorvastatin) which is also proven to have cataractogenic potential. The cases are summarized in the Table below.

Case Number	Age / Gender	Cariprazine Dose	Time to Onset (days)	Time to Discontinuation (days)	Resversibility / Resolution	Location/ side/ severity	Confounding risk factors	Causality by Investigator
#1 RGH-MD-17, PID1051621	40 / M	**1.5 mg**	337	337	**Resolved** at day 374	Unilateral	None	**Related**
#2 RGH-MD-06 PID0110622	41 / M	**9 mg**	28	?	-	Bilateral *PSC* Class II	Previous quetiapine and haloperidol treatment	**Related**
#3 RGH-MD-06, PID 3120610	48 / M	**9 mg**	56	?	**No**	Bilateral	Baseline cataract	Not related / Baseline finding
#4 RGH-MD-06, PID0080614	47 / F	**6 mg**	140 *DB-baseline*	140 (?)	Regression (recovery) at 1 year follow-up	*posterior subcapsular cataract* right eye	concomitant treatment with atorvastatin	**Related** /

#5 **RGH-MD-06, PID60906 03**	48 / F	**3mg**	403	459	**No**	Cataract Class III positive lenticular shifts for both eye "Moderate"	Prior risperidone, haloperidol, zuclopenthixol and chlorpromazine type 2 diabetes mellitus	**Related**
#6 **RGH-MD-06, PID 0080665**	58 / F	**6mg**	143	210 (?)	**No**	bilateral *posterior subcapsular* cataract abnormal cortical nuclear OS Class III positive lenticular shift "moderate"	Age-related changes atorvastatin and quetiapine prior to study enrollment	Not related

Lenticular changes

In Group 1B studies, the pattern of positive lenticular shifts displayed a pattern potentially compatible with a dose-response relation. The highest incidence is seen in the dose-range above the proposed therapeutic range.

Table 2.1.5.12.6-1 Incidence of Lenticular Shifts in Group 1B (Long-term, Open-label Schizophrenia Studies)—Safety Population

	Cariprazine Modal Daily Dose			*Overall Cariprazine N=679 n/N1 (%)*
	1.5-3 mg N=170 n/N1 (%)	*4.5-6 mg N=361 n/N1 (%)*	*9-12 mg N=148 n/N1 (%)*	
Positive lenticular shifts overall				
Class I	7/102 (6.9)	15/239 (6.3)	13/120 (10.8)	35/461 (7.6)
Class II	3/102 (2.9)	9/239 (3.8)	8/120 (6.7)	20/461 (4.3)
Class III	1/102 (1.0)	2/239 (0.8)	6/120 (5.0)	9/461 (2.0)
Positive lenticular shifts at the end of treatment				
Class I	5/102 (4.9)	10/239 (4.2)	13/120 (10.8)	28/461 (6.1)
Class II	4/102 (3.9)	8/239 (3.3)	6/120 (5.0)	18/461 (3.9)
Class III	0/102	1/239 (0.4)	5/120 (4.2)	6/461 (1.3)
Negative lenticular shifts overall				
Class I	13/102 (12.7)	22/239 (9.2)	14/120 (11.7)	49/461 (10.6)
Class II	6/102 (5.9)	10/239 (4.2)	4/120 (3.3)	20/461 (4.3)
Class III	1/102 (1.0)	1/239 (0.4)	1/120 (0.8)	3/461 (0.7)
Negative lenticular shifts at the end of treatment				
Class I	11/102 (10.8)	20/239 (8.4)	13/120 (10.8)	44/461 (9.5)
Class II	3/102 (2.9)	7/239 (2.9)	2/120 (1.7)	12/461 (2.6)
Class III	1/102 (1.0)	1/239 (0.4)	1/120 (0.8)	3/461 (0.7)

In the maintenance of effect study (RGH-MD-06), blurred vision was the most commonly reported ocular AE, reported in 1.4% of patients during the open label phase. Other AEs reported during the study were subcapsular cataract, reported for 3 patients, cataract, diplopia, eye disorder (abnormal cortical nuclear OS), eyelid ptosis, maculopathy, and night blindness, reported for one patient each. Nearly all ocular AEs were mild or moderate in severity, except for 1 report (0.1%) each of severe diplopia and severe

oculogyric crisis. Three patients discontinued treatment during the OL phase due to ocular AEs: 1 patient each with diplopia, oculogyric crisis, and eye swelling and ocular hyperemia (secondary to assault). Three patients discontinued treatment during the double-blind treatment period due to ocular AEs: 1 patient each with cataract, subcapsular cataract, and eye disorder and subcapsular cataract.

In study RGH-MD-06, concerning the LOCSIII data, in the run-in phase and double-blind phase Class III positive lenticular shifts were observed for 6 of 212 patients (2.8%) at the end of the open label phase, and 3 of 48 patients (6.3%) in the cariprazine 3-6 mg modal daily dose group and 2 of 89 patients (2.2%) in the placebo group (Table 44.3). This imbalance is notably very sensitive to random error since only one less cariprazine exposed case and two more placebo exposed cases would completely equalise the balance between cataract cases.

Table 44.3 Incidence of Lenticular Shifts at the End of the Treatment Periods—Run-in Phase Safety Population and Double-blind Safety Population

	Open-label Phase	*Double-blind Period*	
	Cariprazine 3-6 mg (N=337) n/N1 (%)	***Placebo (N=99) n/N1 (%)***	***Cariprazine 3-6 mg (N=51) n/N1 (%)***
Positive lenticular shifts at the end of the treatment period			
Class I	7/212 (3.3)	10/89 (11.2)	5/48 (10.4)
Class II	2/212 (0.9)	4/89 (4.5)	1/48 (2.1)
Class III	6/212 (2.8)	2/89 (2.2)	3/48 (6.3)
Negative lenticular shifts at the end of the treatment period			
Class I	4/212 (1.9)	2/89 (2.2)	2/48 (4.2)
Class II	4/212 (1.9)	3/89 (3.4)	1/48 (2.1)
Class III	2/212 (0.9)	0/89	1/48 (2.1)

LOCS III = Lens Opacities Classification System III; N= Number of patients in Placebo group; number of patients in Cariprazine treatment with modal daily dose of 3-6 mg, n = number of patients in each category, N1 = number of patients with nonmissing baseline and at least one postbaseline LOCS III assessment.

In negative symptoms study (RGH-188-005), 3 patients in the cariprazine group and 4 patients in the risperidone group ocular AEs were reported. No differences between the treatment groups in frequency, severity, or relationship of AEs to study drug were clinically meaningful. None of the eye disorder AEs was an SAE. Four patients who had positive or negative shifts in LOCS III grading experienced ocular AEs; 1 patient was in the cariprazine group and 3 patients were in the risperidone group (Table 2.1.5.12.6-5.).

Table 2.1.5.12.6-4 Number and Percentage of Patients with Positive or Negative Lenticular Shifts, Safety Population

Parameter	*Cariprazine N=230 n (%)*	*Risperidone N=230 n (%)*
Number of patients assessed at Week 26/ET	199	193
Positive lenticular shifts at the end of the treatment period		
Class I	8 (4.0)	4 (2.1)
Class II	4 (2.0)	1 (0.5)
Class III	2 (1.0)	2 (1.0)
Negative lenticular shifts at the end of the treatment period		
Class I	4 (2.0)	5 (2.6)
Class II	4 (2.0)	7 (3.6)
Class III	0	1 (0.5)

LOCS III = Lens Opacities Classification System III; N1 = number of patients with nonmissing baseline and at least one postbaseline LOCS III assessment at the end of the open-label phase

In short-term controlled mania studies (Group 2A), blurred vision was reported more frequently in the cariprazine group (3.7%) than in the placebo group (1.1%). All other ocular AEs were reported for < 1% of patients in any group without a dose-response relationship. AEs related to reductions in visual acuity, colour vision, cataract, or lens opacities were not observed.

In the long-term mania study (Group 2B), the most commonly reported ocular AEs were blurred vision and dry eye. All other ocular AEs were reported for < 1% of patients overall. No patient had AEs related to visual acuity or colour vision. 1 patient had an AE of cataract. The findings of LOCSII data were in line with the long-term schizophrenia data: both positive and negative shifts were observed, five of these shifts were of Class III (Table 2.1.5.12.6-3).

Table 2.1.5.12.6-3 Incidence of Lenticular Shifts in Group 2B (Long-term, Open-label Bipolar Mania Study)—Safety Population

	Cariprazine Modal Daily Dose		*Overall Cariprazine (N = 402) n/N1 (%)*
	3-6 mg (N = 234) n/N1 (%)	*9-12 mg (N = 168) n/N1 (%)*	
Positive lenticular shifts at the end of treatment			
Class I	4/176 (2.3)	7/133 (5.3)	11/309 (3.6)
Class II	2/176 (1.1)	2/133 (1.5)	4/309 (1.3)
Class III	2/176 (1.1)	3/133 (2.3)	5/309 (1.6)
Negative lenticular shifts at the end of treatment			
Class I	7/176 (4.0)	3/133 (2.3)	10/309 (3.2)
Class II	4/176 (2.3)	2/133 (1.5)	6/309 (1.9)
Class III	2/176 (1.1)	1/133 (0.8)	3/309 (1.0)

LOCS III = Lens Opacities Classification System III; N1 = number of patients with nonmissing baseline and at least 1 postbaseline LOCS III assessment or with cataract surgery

In bipolar depression studies, the frequency of ocular TEAEs was 1.8% in the placebo group and 2.4% in the overall cariprazine group with the most common ocular TEAE blurred vision, which was reported in 0.4% of patients in the placebo group, and 0.9% of patients in the cariprazine group. All ocular TEAEs were reported for < 1% of patients in any treatment group. No SAEs or discontinuation due to an ocular AE was reported.

In major depressive disorder studies, ocular TEAEs were reported more frequently in the overall cariprazine group (3.7%) than in the placebo group (1.4%). The most commonly reported ocular TEAE was blurred vision (0.9% in placebo group, 2.3% in the cariprazine group). All other ocular TEAEs were reported for < 1% of patients. No serious or severe ocular AEs were reported. Two patients discontinued treatment due to ocular AEs, 1 patient on placebo with mild age-related macular degeneration (ongoing at time of discontinuation), and 1 patient discontinued because of AEs of fatigue, insomnia, and moderate blurred vision.

Pooled data for LOCSIII results from studies including Group 1B (RGH-MD-17 and RGH-MD-11), the maintenance of efficacy study (RGH-MD-06), the negative symptoms study (RGH-188-005) and the long-term mania study (Group 2B, RGH-MD-36) and RGH-MD-04 and RGH-MD-05 are summarized in the Table below.

Table 6.1 Incidence of Lenticular Shifts at any point of the Treatment in Pooled Long Term Studies - Safety Population

Parameter	*Placebo (N=403)*	*Cariprazine 1.5 - 6 mg (N=1724)*	*Aripiprazole 10 mg (N=152)*	*Risperidone 4 mg (N=230)*
Negative lenticular shifts				
Class I	7 / 224 (3.1)	46 / 749 (6.1)	1 / 62 (1.6)	0 / 16
Class II	3 / 224 (1.3)	32 / 749 (4.3)	0 / 62	2 / 16 (12.5)
Class III	0 / 224	6 / 749 (0.8)	0 / 62	0 / 16
Positive lenticular shifts				
Class I	13 / 224 (5.8)	42 / 749 (5.6)	2 / 62 (3.2)	1 / 16 (6.3)
Class II	4 / 224 (1.8)	22 / 749 (2.9)	0 / 62	0 / 16
Class III	9 / 224 (4.0)	12 / 749 (1.6)	0 / 62	0 / 16

Source: Appendix EU-180, Table 13.9.1

Note: This analysis includes the mania study RGH-MD-36, and reflects changes not only from baseline to end but to any time-point during treatment.

There were more negative lenticular shifts (improvement) observed for cariprazine and risperidone; whereas more positive shifts (worsening) were observed for placebo and aripiprazole. Highest rates in positive shifts were observed for placebo: Class I shifts (5.8%), Class II (1.8%) and Class III (4%). For cariprazine, positive Class I shifts were observed in 5.6%, Class II in 2.9% and Class III in 1.6% of patients. Overall, the net effect of shifts for cariprazine was negative shifts, while the occurrence of positive shifts was comparable with placebo.

Best-Corrected Visual Acuity

Best-Corrected Visual Acuity (BCVA) testing was implemented in Studies RGH-MD-04 and RGH-MD-05, the cariprazine long-term studies of Group 1B (RGH-MD-17 and RGH-MD-11), the maintenance of efficacy study (RGH-MD-06), the negative symptoms study (RGH-188-005) and the long-term mania study (Group 2B, RGH-MD-36). Table below presents BCVA data for the schizophrenia program by dose. Based on the data below, no divergent effect was detected on BCVA with cariprazine compared to placebo or active comparators.

Table 41. Best-Corrected Visual Acuity Data in the schizophrenia program by dose and overall claimed posology— Safety Population

System Organ Class Preferred Term	*Placebo (N 683) n (%)*	*Cariprazine Modal Daily Dose*				*Cariprazine Claimed posology (N =2048) n (%)*	*Risperidone 4 mg (N =370) n (%)*	*Aripiprazole 10 mg (N =152) n (%)*
		1.5 mg (N 180) n (%)	*3 mg (N 619) n (%)*	*4.5 mg (N 549) n (%)*	*6 mg (N 794) n (%)*			
BCVA right eye								
Baseline								
N	322	7	302	212	576	1043	186	129
Mean	0.09	0.03	0.08	0.10	0.10	0.09	0.22	0.14
Std. Dev.	0.24	0.08	0.21	0.30	0.24	0.24	1.51	0.29
Endpoint								
N	322	7	302	212	576	1043	186	129
Mean	0.07	0.02	0.07	0.10	0.08	0.08	0.09	0.12
Std. Dev.	0.20	0.09	0.22	0.27	0.22	0.23	0.33	0.28
Change from baseline								
N	322	7	302	212	576	1043	186	129
Mean	**-0.02**	**-0.01**	**-0.01**	**-0.01**	**-0.02**	**-0.01**	**-0.13**	**-0.01**
Std. Dev.	0.15	0.04	0.15	0.19	0.17	0.17	1.49	0.17
BCVA left eye								
Baseline								
N	322	7	302	212	576	1043	186	129
Mean	0.09	0.02	0.09	0.12	0.09	0.10	0.21	0.15
Std. Dev.	0.23	0.09	0.23	0.28	0.24	0.24	1.51	0.30
Endpoint								
N	322	7	302	212	576	1043	186	129
Mean	0.07	0.03	0.09	0.10	0.08	0.08	0.09	0.13
Std. Dev.	0.21	0.09	0.23	0.26	0.22	0.23	0.34	0.29
Change from baseline								
N	322	7	302	212	576	1043	186	129
Mean	**-0.01**	**0.01**	**-0.01**	**-0.03**	**-0.01**	**-0.01**	**-0.12**	**-0.02**
Std. Dev.	0.15	0.04	0.15	0.15	0.18	0.17	1.49	0.18

N=number of patients in the safety population, n (%) = number and percentage of patients with specified event,

Retinal toxicity

In the overall cariprazine development program, retinal toxicity related TEAEs (retinal degeneration, retinal pigment epithelium detachment, retinal detachment) were reported for 2 patients treated with cariprazine, 1 patient treated with risperidone and 1 patient treated with placebo and all had confounding risk factors.

Phospholipidosis

Phospholipidosis was observed in the non-clinical studies in lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal gland cortex of dogs at clinically relevant exposures (AUC) of total cariprazine (see Non-clinical section of this report). The analysis of the clinical database with regard to respiratory/pulmonary symptoms did not yield a pulmonary safety signal associated with exposure to cariprazine. Based on the toxicological findings, and assuming that they would translate into similar findings in humans, one would expect possible manifestations of inflammatory processes, which may possibly detected by the clinical symptoms of cough, dyspnoea, fatigue, and elevation in basophils, monocytes, or leucocytes. The analysis of the clinical database with regard to AEs of the high-level group

term “adrenal gland disorders” and cortisol abnormalities, adrenal insufficiency, adrenal suppression, weakness, fatigue, malaise, depression, nausea, vomiting, anorexia, weight loss, hyperpigmentation, hypotension, hyponatremia, hyperkalemia, electrolyte abnormality, and eosinophilia, did not reveal a pattern indicative of adrenal dysfunction. Specific assessments of adrenocorticotrophic hormones were not performed in the cariprazine clinical program. The events identified in the database search were nonspecific events, such as nausea, vomiting, and fatigue, which are commonly seen with antipsychotic therapy. Few patients had concurrent events. There was no correlation of the identified events with other clinical findings. There were no events of cortisol abnormalities, adrenal insufficiency, or adrenal suppression. One patient had an AE from the adrenal gland disorder term adrenal adenoma which was not judged to be related to the treatment.

Body weight changes

Changes in body weight have been observed with cariprazine treatment. Mean change from baseline in body weight in the short term studies was 0.9 kg, while in the long term studies it was -0.3 kg in RGH-188-005 (26 weeks, RGH-188-005), 1.8 kg in Group 1B studies (48 weeks) and 0.6 kg in RGH-MD-06 (up to 92 weeks). Overall, taking all studies into account, a slight weight increase of 0.9 kg with cariprazine was observed.

Based on the measurements, potentially clinically significant (PCS) changes in body weight (≥ 7% increase or ≥ 7% decrease) have been observed. For the cariprazine treated patients, 7% in short-term studies and up to 28% in long-term open-label safety studies weight gain was observed within the claimed posology, while for risperidone treated patients this was 16% in short-term studies. In the open-label phase of study RGH-MD-06 during 20 weeks cariprazine treatment 9.0% of patients developed potentially clinically significant (PCS) weight gain (defined as increase ≥ 7%) while during the double-blind phase, 9.8 % of the patients who continued with cariprazine treatment had PCS weight gain versus 7.1% of the patients who were randomized to placebo after the 20 week open-label cariprazine treatment. In the negative symptom study RGH-188-005, the PCS weight gain was observed in 6% of the cariprazine group while 7.4% of the risperidone group.

Although, the frequency of reported weight related TEAEs were relatively lower compared to the frequency of PCS weight gain in all studies and all treatment groups up to the frequency of 11.5% weight increased was reported in the long-term studies related to cariprazine in Group 1B open-label safety studies. Interestingly, no weight increased TEAEs were reported during the double-blind period of the maintenance of effect study, RGH-MD-06. Lower frequencies of weight increased TAEs were reported for both risperidone and cariprazine in the negative symptom study, RGH-MD-188-005.

Metabolic parameters

In Group 1A studies, there were no deaths or SAEs associated with metabolic changes, while one patient discontinued the study due to AEs blood glucose increased and blood triglycerides increased.The incidence of patients with TEAEs associated with hyperlipidaemia was approximately 1% across all treatment groups. The incidence of patients with TEAEs associated with hyperglycemia and diabetes mellitus was < 1% with cariprazine and 1% with placebo.

The incidence of treatment-emergent significant changes in metabolic parameters tended to increase over time in Group 1B open-label long term studies. Approximately 5% of Group 1B patients had treatment-emergent glycosuria and approximately 7% had treatment-emergent significant shifts in glycosylated haemoglobin. There was no death associated with metabolic changes. However, one patient (with history of Type 2 diabetes mellitus) had a SAE of diabetes mellitus inadequate control that was

considered to be related. No patient in Group 1B discontinued the study due to metabolic changes. Hyperlipidaemia was detected in in 3% of patients while 1% had hyperglycemia and diabetes mellitus TEAEs. One patient had TEAEs of type 2 diabetes mellitus and metabolic syndrome judged as possibly related to cariprazine and another patient had an SAE of diabetes mellitus inadequate control as described above related to cariprazine.

In the RGH-MD-06, maintenance of effect study, the highest frequency of TEAE related to metabolic changes were blood triglycerides increased with 4% in cariprazine group during the double blind period, followed by 3% for diabetes mellitus both in open label and double blind phase in the cariprazine group. There were no deaths, nor SAEs and no discontinuations associated with metabolic changes (hyperlipidaemia, hyperglycemia or diabetes mellitus) in Study RGH-MD-06 and RGH-188-005.

Suicidality

Suicidality was assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS). Throughout the cariprazine development program, 6 death cases occurred due to completed suicide, but none were judged to be related to cariprazine. In the schizophrenia studies, 17 SAEs of the suicidality category were reported. In the PK/PD studies there were no TEAEs of suicidal ideation. In the mania studies Group 2A, 4 placebo-treated (0.9%), 2 cariprazine-treated patients (0.3%), in Group 2B 8 cariprazine-treated patients (2%) had suicidality TEAEs. In the bipolar depression studies, 8 patients (1.4%) in the overall cariprazine group and 3 patients (1.4%) in the placebo group had TEAEs of suicidal ideation. In the major depressive disorder studies there were no completed suicides; but 1 patient (0.1%) in the overall cariprazine group had a TEAE of suicidal ideation.

Seizures / convulsion

In Group 1A studies, 3 patients in the placebo group (0.5%) and one patient in cariprazine dose group 4.5-6 mg dose group (0.1%) and one aripiprazole (0.7%) groups had TEAEs of seizure or convulsion. The case in the cariprazine group was judged as possibly related.

In Group 1B studies, 1 patient (0.1%) had a TEAE of the seizure/convulsion category and was judged as not related to cariprazine treatment. In the maintenance of effect study (RGH-MD-06) 1 patient had a SAE of the seizure / convulsion in the screening period before receiving any investigational product, one patient had a TEAE of convulsion in the open label-treatment phase which was judged to be related with confounding factors, one patient in the safety follow phase after premature discontinuation from the open-label phase and one patient in the double blind phase. In the negative symptoms study (RGH-188-005) there was no reported TEAE of seizure / convulsion.

In the PK/PD studies there was no reported TEAE of seizure/convulsion. In the bipolar mania program 2 cariprazine-treated patients (0.3%) had TEAEs of convulsion during the double-blind treatment period of the controlled mania studies. Both events were serious, led to premature study discontinuation, and were judged by the Investigator to be related to treatment with cariprazine. In Group 2B, no TEAE of seizure or convulsion was reported during the open-label treatment period. There was 1 report of seizure during the safety follow-up period, which the Investigator assessed as no serious, moderate in intensity, and unrelated to cariprazine. In the bipolar depression and major depressive disorder studies there were no TEAEs of seizure/convulsion.

Neuroleptic Malignant Syndrome, Serotonin syndrome and Hyperthermia

No TEAE of Neuroleptic malignant syndrome, Serotonin syndrome and Hyperthermia malignant was reported in Group 1A, 1B or RGH-188-005 studies. In Study RGH-MD-06, there was one TEAE of neuroleptic malignant syndrome in the open-label phase. There was no TEAE of neuroleptic malignant syndrome in the PK/PD studies, in the bipolar mania, bipolar depression or major depressive disorder studies.

Deep Vein Thrombosis/Pulmonary Embolism Events

No patient had TEAE of deep vein thrombosis or pulmonary embolism in the schizophrenia studies. One cariprazine treated patient in Group 1B had thrombophlebitis. One patient in RGH-06 study experienced thrombocytosis. In the mania studies, two cariprazine-treated patients had adverse events: a pulmonary embolism resulting in death and a SAE of deep vein thrombosis that was detected during the safety-follow-up period.

Cognitive Impairment and Delirium

In the cariprazine schizophrenia program, there were 11 (0.5%) TEAEs associated with cognition, 8 (0.4%) of which were considered by the Investigators as related to treatment. Cognition related TEAEs were reported in 1.0% of patients in the claimed posology. In the short term controlled studies the incidence of cognition related TEAEs was 0.4% in the cariprazine group, 0.2% in the placebo group and higher in the comparators groups: risperidone 0.7% and aripiprazole 0.7%. In the long term study RGH-MD-06 the incidence of cognition related TEAE in the placebo group was 1.0% while in the cariprazine group it was 0%. In study RGH-188-005 the incidence of cognition related TEAEs was 0.9% for cariprazine and 0.4% for risperidone. Overall frequencies of cariprazine's cognition –related TEAEs were similar to placebo and uncommon.

Table 107.1 Cognitive and mental adverse events during cariprazine treatment in the claimed posology

TEAE type	*Schizophrenia n=2048*	*Bipolar Mania n=497*	*Bipolar Depression n=367*	*Major Depressive Disorder n=482*	*PK/PD studies n=162*	*Total n=3556*
Any TEAE of this category	**11 (0.5)**	**9 (1.8)**	**5 (1.4)**	**9 (1.9)**	**2 (1.2)**	**36 (1.0)**
TEAEs that were drug related	**8 (0.4)**	**6 (1.2)**	**5 (1.4)**	**8 (1.7)**	**2 (1.2)**	**29 (0.8)**
Disturbance in attention	3 (0.1)	4 (0.8)	3 (0.8)	7 (1.5)	2 (1.2)	19 (0.5)
Mental impairment	3 (0.1)	0 (0.0)	2 (0.5)	2 (0.4)	0 (0.0)	7 (0.2)
Confusional state	3 (0.1)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Delirium	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Memory impairment	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)
Disorientation	1 (0.0)	-	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Mental status changes	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Cognitive disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Appendix EU-MAA, Tables 7.4.29.1, 7.4.29.2, 7.4.29.3, 7.4.29.4, 7.4.29.5A, 7.4.29.5B, 7.4.29.5C, 7.4.29.5D, 7.4.29.5E

Cerebrovascular disease

One SAE of ischemic stroke was reported after study discontinuation leading to death in schizophrenia studies. In PK/PD and studies in other indications 2 aphasia cases, 7 cases with dysarthria and 1 brain injury case were reported. Most cases were judged by the Investigator as mild or moderate in intensity (except for one case of dysarthria which was judged as severe) and related to treatment. No TEAE of this category was judged as SAE.

Sedation

The incidence of sedation related TEAEs in the short term schizophrenia trials (Group 1A) was 7.5% in the cariprazine group and 5.8% in the placebo group. The incidence of sedation related TEAEs was 7.1% in Group 1B, and 5.2% in the open label phase of study RGH-MD-06. During the double-blind phase the incidence of sedation related TEAEs was 3% for cariprazine and 0 for placebo. When cariprazine was compared to risperidone over a time of 26 weeks, the incidence of sedation grouped AEs was 5.2% for cariprazine and 6.0% for risperidone.

In the PK/PD studies performed in healthy volunteers the incidence of sedation grouped TEAEs was 17.4% for placebo and 9.4% for cariprazine, in schizophrenic patients the incidence was 25.3% for placebo and 36.6% for cariprazine. In the mania studies the incidence was 4.0% for placebo and 8.0% for cariprazine and 8.7% for open-label cariprazine in the long-term mania study. In the BD studies the incidence was 6.3% for placebo and 6.0% for cariprazine. In the MDD studies the incidence was 4.8% for placebo and 9.4% for cariprazine. Overall, the incidence of sedation related TEAEs in controlled studies was 11.4% for cariprazine and 9.1% for placebo.

Sexual dysfunction

In the cariprazine schizophrenia program, there were 21 (1.0%) TEAEs associated with sexual dysfunction.

Table 108.1 Adverse events related to sexual dysfunction during cariprazine treatment in the claimed posology

TEAE type	*Schizophrenia n=2048*	*Bipolar Mania n=497*	*Bipolar Depression n=367*	*Major Depressive Disorder n=482*	*PK/PD studies n=162*	*Total n=3556*
Any TEAE of this category	**21 (1.0)**	**8 (1.6)**	**5 (1.4)**	**7 (1.5)**	**0 (0.0)**	**41 (1.2)**
TEAEs that were drug related	**20 (1.0)**	**5 (1.0)**	**4 (1.1)**	**7 (1.5)**	**0 (0.0)**	**36 (1.0)**
Erectile dysfunction	6 (0.4)	2 (0.7)	4 (2.9)			12 (0.3)
Libido decreased	6 (0.3)	2 (0.7)		4 (0.8)		12 (0.3)
Libido increased	3 (0.1)	3 (0.6)		2 (0.4)		8 (0.2)
Anorgasmia	1 (0.0)			1 (0.2)		2 (0.1)
Ejaculation failure	1 (0.1)			1 (0.8)		2 (0.1)
Female orgasmic disorder	1 (0.2)					1 (0.0)
Painful erection	1 (0.1)					1 (0.0)
Ejaculation disorder	1 (0.1)					1 (0.0)
Sexual dysfunction	1 (0.0)					1 (0.0)
Hypersexuality		1 (0.2)				1 (0.0)
Ejaculation delayed			1 (0.7)			1 (0.0)
Orgasm abnormal			1 (0.3)			1 (0.0)

Autonomic nervous system disorders

14% of cariprazine treated patients in Group 1A, 13% of patients in Group 1B, 14% of cariprazine treated patients in study RGH-MD-06 in the open-label and 10 % in the double blind group had TEAEs related to autonomic nervous system disorders, In study RGH-188-005 approximately 4% of patients in both treatment groups had TEAEs related to autonomic nervous system disorders. Dizziness, syncope and blurred vision were the most frequent autonomic nervous system disorder related TEAEs in Group 3A. In Group 3B orthostatic hypotension and orthostatic tachycardia were also among the more common TEAEs associated with autonomic nervous system disorders. Approximately 20% of manic patients, 11% of bipolar depression patients and 12% of major depressive disorder patients had TEAEs associated with autonomic nervous system disorders.

Prolactin

No TEAEs related to elevation of prolactin levels was reported in cariprazine-treated patients in the clinical studies. Mean decreases in prolactin levels from baseline were seen in all treatment groups, with the exception of the risperidone group. No AEs of hyperprolactinemia were reported.

Renal Safety

Overall, there were no deaths, no SAEs and no discontinuations related to renal functioning. In group 1A studies, one TEAE of proteinuria and one hemorrhage in the urinary tract were reported in the 9-12 mg/day cariprazine group. In Group1B, one renal failure was reported in association with the

rhabdomyolysis case, one patient with blood urea increased, one patient with blood uric acid increased, one patient with haematuria and one patient with urinary retention in association to rhabdomyolysis. In RGH-MD-06, one cariprazine treated patient had TEAE of blood uric acid increased. In RGH-188-005 one cariprazine treated patient had a TEAE of haematuria and renal colic.

ECG and QT Interval

The effect of 9 mg/day and 18 mg/day cariprazine on cardiac repolarization was investigated in a multicentre, randomized, double-blind, placebo, and moxifloxacin-controlled, parallel-group study in patients with schizophrenia. There was no evidence that cariprazine results in statistically or clinically significant QTc prolongation following 9 mg/day, the highest tested dose in confirmatory trials to show efficacy, and a supra therapeutic dose (18 mg/day). No patients treated with cariprazine experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec in the study (RGH-MD-02). In a population PK-PD analysis, data from 11 studies were used to quantitatively evaluate the potential for QTcF prolongation by cariprazine plasma exposures. No clinically meaningful relationship between total cariprazine plasma concentrations and QTcF prolongation over the dose range of 0.5 to 21 mg/day was found (RGH-MS-02).

Small mean increases from baseline in ventricular heart rate were observed with cariprazine therapy, relative to placebo, consistent with the mean changes observed in pulse rate. Post baseline QTcF values > 500 msec was seen in only 1 patient, in the long-term schizophrenia studies. The percentages of patients with an increase from baseline of > 60 msec in QTcF values were low in the cariprazine groups and similar to those in the placebo groups (≤ 0.5%). No AEs of torsade de pointes, ventricular fibrillation, or ventricular tachycardia were reported.

During the long-term, open-label treatment period in Group 1B, 3 patients (0.4%) had QTcB > 500 msec, one of whom also had QTcF > 500 msec. A > 60 msec increase from baseline was observed in 7 patients (1%) for QTcB and in 2 patients (0.3%) for QTcF. No dose-response pattern was observed when the data were examined by modal daily dose.

The most common TEAEs associated with ECG findings were sinus tachycardia (6 patients, 0.9%), electrocardiogram QT prolonged (5 patients, 0.7%), and sinus bradycardia (4 patients, 0.6%). Two patients (0.3%) each had TEAEs of bundle branch block left, electrocardiogram T wave inversion; and 1 patient (0.1%) each had a TEAE of supraventricular extrasystoles, atrioventricular block I, electrocardiogram T wave abnormal, electrocardiogram ST-segment depression, electrocardiogram T wave amplitude decreased, and sick sinus syndrome.

In RGH-MD-06, maintenance of effect study, no patient had post baseline QTcB or QTcF > 500 msec. During the open-label phase, > 60 msec increase of from baseline was observed in 12 patients (1.6%) for QTcB and in 4 patients (0.5%) for QTcF. During the double-blind treatment period, > 60 msec increases from baseline in QTcB were observed in 3 cariprazine-treated patients (3.1%) and 2 placebo-treated patients (2%). For the six cariprazine treated patients with an increase from baseline QTcF of > 60 msec in both treatment periods, the increase was only a single occurrence; changes from baseline in QTcF at all other assessments were always < 60 msec. No dose-response relationship was observed among the cariprazine modal daily dose groups.

There were no ECG related SAEs. SAEs of atrial fibrillation, sinus tachycardia, tachycardia paroxysmal were reported for placebo treated patients. One cariprazine treated patient in the open-label phase and one placebo treated patient discontinued the study due to ECG related TEAEs.

In RGH-188-005, no patient had post-baseline QTcB or QTcF > 500 msec and no patients had increases of 30 or 60 msec from baseline in QTcB or QTcF parameters. The numbers of TEAEs related to ECG abnormalities were small in both treatment groups. None of these TEAEs were SAEs or discontinuations.

Reproductive toxicity

The clinical trials included only female patients of non-childbearing potential or non-pregnant, not breast-feeding women of childbearing potential, using reliable contraception. The study was prematurely discontinued if a patient got pregnant. Despite that, during the cariprazine development program a total of 22 pregnancies were reported; 13 of these occurred in cariprazine-treated patients. Based on the narratives of these pregnancies; 7 delivered a healthy baby, one delivered pre-term tiplets, one delivered baby experienced pneumonia with sepsis, , 4 had unknown outcome, 4 underwent induced abortion, 2 elective abortion and 2 ended with spontaneous abortion one of which was due to intrauterine fetal death.

Serious adverse event/deaths/other significant events

SAEs were reported for 6.6% of cariprazine treated patients in the claimed posology and 8.2% of placebo treated patients. No clear dose dependency was observed for any of the SAEs. Schizophrenia and psychotic disorder were the most commonly reported SAEs, with a higher incidence in the placebo group (5.1%) than in the cariprazine group (3.1%), indicating relapse of schizophrenic symptoms. All other SAEs were reported in less than 1% of patients.

Table 42. Serious Adverse Events in cariprazine treated patients in all schizophrenia studies (safety population)

Table 92.1 Serious Adverse Events in > 1 Cariprazine Treated Patient in all Schizophrenia Studies — Safety Population

System Organ Class Preferred Term	*Placebo (N 683) n (%)*	*Cariprazine Modal Daily Dose*				*Cariprazine Claimed posology (N 2048) n (%)*	*Risperidone (N 370) n (%)*	*Aripiprazole (N 152) n (%)*
		1.5 mg (N 180) n (%)	*3 mg (N 619) n (%)*	*4.5 mg (N 549) n (%)*	*6 mg (N 794) n (%)*			
Patients with ≥ 1 SAE	**56 (8.2)**	**10 (5.6)**	**37 (6.0)**	**29 (5.3)**	**59 (7.4)**	**135 (6.6)**	**12 (3.2)**	**4 (2.6)**
Cardiac disorders								
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.1)	0 (0.0)	0 (0.0)
Infections and infestations								
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)
Pneumonia	2 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders								
Hyponatremia	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Nervous system disorders								
Psychomotor hyperactivity[a]	3 (0.4)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	3 (0.1)	0 (0.0)	0 (0.0)
Psychiatric disorders								
Schizophrenia	24 (3.5)	4 (2.2)	12 (1.9)	10 (1.8)	18 (2.3)	44 (2.1)	5 (1.4)	0 (0.0)
Psychotic disorder	11 (1.6)	1 (0.6)	10 (1.6)	3 (0.5)	7 (0.9)	21 (1.0)	2 (0.5)	0 (0.0)
Schizophrenia, paranoid type	1 (0.1)	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.4)	6 (0.3)	0 (0.0)	0 (0.0)
Agitation	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	1 (0.1)	5 (0.2)	0 (0.0)	0 (0.0)
Suicidal ideation	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.3)	4 (0.2)	0 (0.0)	0 (0.0)
Acute psychosis	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Completed suicide	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)
Hallucination, auditory	2 (0.3)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Psychotic behaviour	3 (0.4)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Social circumstances								
Social stay hospitalization	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.2)	6 (0.8)	9 (0.4)	0 (0.0)	1 (0.7)

N=number of patients in the safety population, n (%) = number and percentage of patients with specified event, SAE = serious adverse event.
Source: Appendix EU-120, Table 6.5.13

SAEs related to AEs of special interest for cariprazine are summarized below. SAEs were observed for suicidality grouped TEAEs, seizures and convulsions, cerebrovascular and cardiovascular diseases and CPK/rhabdomyolysis in the cariprazine claimed posology group.

Table 43. SAEs related to adverse events of special interest

Table 92.2 SAEs related to adverse events of special interest

Prefered Term	Number of patients with SAE in the category
Suicidality	8
EPS (dyskinesia, dystonia, parkinsonoid, akathisia, restlessness tardive dyskinesia)	0
Seizures/ convulsions	2
Neuroleptic malignant syndrome (NMS)	0
Deep vein thrombosis/ Pulmonary embolism	0
Cognitive impairment and Delirium	0
Cerebrovascular disease	2
Sedation	0
Sexual dysfunction	0
Autonomic nervous system disorders (Orthostatic hypotension, enuresis, vasomotor rhinitis, temperature changes, hypersalivation, dry mouth)	0
Prolactine increase	0
Cardiovascular disease/sudden death/QT prolongation (causes ventricular arrhythmia, torsades de pointes)	7
Weight increase/metabolic syndrome/Body weight changes either way	0
Haematopoetic changes (leucocytosis, leucopenia (agranulocytosis), eusinophilia)	0
Liver enzyme increase/ ALT/AST elevations	1
Rhabdomyolysis (muscle pain, weakness, CPK increase, renal failure due to myoglobin set free from damaged muscle cells, Myoglobulinurie)	2
Ocular effects (cataract, retinal degeneration, atrophy)	0
Phospholipidosis/fibrosis	0
Cholesterol/Triglyceride decreases	0
Reproductive toxicity	0
Increase in blood pressure	1

Table 92.3 SAEs in Adverse Events of Special Interest in all Schizophrenia Studies — Safety Population

System Organ Class Preferred Term	*Placebo (N 683) n (%)*	*Cariprazine Modal Daily Dose*				*Cariprazine Claimed posology (N 2048) n (%)*	*Risperidone (N 370) n (%)*	*Aripiprazole (N 152) n (%)*
		1.5 mg (N 178) n (%)	*3 mg (N 620) n (%)*	*4.5 mg (N 548) n (%)*	*6 mg (N 796) n (%)*			
Suicidality								
Completed suicide	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	1 (0.3)	0 (0.0)
Intentional overdose	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.3)	0 (0.0)
Suicidal ideation	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.3)	4 (0.2)	0 (0.0)	0 (0.0)
Seizures/ convulsions								
Complex partial seizures	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Grand mal convulsion	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Convulsion	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Generalised tonic-clonic seizure	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Status epilepticus	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular disease								
Ischaemic stroke	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular disease/sudden death/QT prolongation								
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.1)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block second degree	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Sick sinus syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Chest pain	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.3)	0 (0.0)
Increase in blood pressure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)
Liver enzyme increase; ALT/AST elevations								
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0,1)	1 (0.0)	0 (0.0)	0 (0.0)
Rhabdomyolysis/CPK								
Blood CPK increased	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.3)	0 (0.0)
Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)

N=number of patients in the safety population, n (%) = number and percentage of patients with specified event, SAE = serious adverse event.
Source: Appendix EU-120, Table 6.5.13

Overall, 17 deaths were reported in the cariprazine development program. Of these, only 11 patients received at least 1 dose of cariprazine, 3 occurred in the Phase II/III schizophrenia program and only one death case was considered by the Investigator to be related to cariprazine. This case was a 36-year-old male with history of schizophrenia, low body weight (BMI 16.2) and concomitant common cold who received cariprazine for 4 days. Cariprazine was up-titrated according to protocol, with the patient receiving 1.5mg on day 1 (experiencing transient nausea), 3mg on day 2, 4.5mg on day 3 (experiencing transient diarrhoea) and 6 mg on day 4. On day 4, hours after study drug intake, the patient was discovered in a cardiopulmonary arrest state, and died on the same day. Due to the temporal relationship between drug intake and occurrence of death the Investigator considered the case to be related to study drug. However, the study data safety monitoring board pointed out various confounding factors (rapid weight gain in a patient with screening low BMI, concomitant common cold and diarrhoea one day before the event). Other possible confounding factors include zopiclone, hypokalaemia effects of tsumura kakkonto herbal extract and prior ECG findings of abnormal Q wave, ST elevation, and atrial fibrillation in this patient. No obvious causality between the study drug and the deaths can be claimed.

Discontinuation due to AES

The overall incidence of discontinuation due to AEs was 12.1 % in the cariprazine groups within claimed posology compared to 12.4 % of placebo treated patients. Schizophrenia and psychotic disorder were the most common TEAEs leading to study discontinuation, with a higher incidence in the placebo group compared to the cariprazine group. All other discontinuations were reported in less than 1 % of patients. Discontinuations due to adverse events of special interest were reported in less than 0.1 % within the claimed cariprazine posology group. Of these akathisia (0.9%), suicidal ideation (0.3%), EPS (0.2%) and female orgasmic disorder (0.2%) had highest incidences, while one case each of cataract and subcapsular cataract were reported as AE leading to discontinuation.

Overdose

The maximum tolerated dose of cariprazine in patients with schizophrenia or schizoaffective disorder was 18 mg/day. Few instances of overdose, in the clinical databases of the schizophrenia studies and none of the patients who received cariprazine greater than 18 mg/day experienced an adverse outcome. One accidental overdose of cariprazine with 48 mg experienced orthostatic dizziness and sedation, however fully recovered the same day.

Safety related to drug-drug interactions and other interactions

Cariprazine is metabolized to its active metabolites DCAR and DDCAR with both CYP3A4 and CYP2D6 enzymes involved. Thus, inhibitors and inducers of CYP3A4 might influence the formation of the active metabolites, and elimination of the mother substance. However, there are uncertainties concerning how DCAR and DDCAR are eliminated. Therefore, based on current information available, the safety of drug interactions is not completely clear. Moreover, there are questions concerning the potential impact of CYP2D6 metabolizer status on safety of cariprazine. There are additional uncertainties concerning how cariprazine would influence other drugs as a Pgp inhibitor.

Currently, based on the available knowledge no firm conclusions can be drawn concerning the safety of drug-drug interactions with cariprazine.

Post marketing experience

Cariprazine was approved by the FDA on 17 Sep 2015 for treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder using the trade name Vraylar. The product was marketed in the US from March 5th 2016. According to the post-approval data from the US, the cumulative patient exposure of cariprazine from product launch (March 5th, 2016) to February 24th, 2017 is estimated to be 11668 patient-years. It is noted that patient-years may underestimate actual patient numbers since compliance and persistency are not factored into calculations.

Overall, 100 ICSRs with 215 Adverse Drug Reactions (ADRs) were received concerning cariprazine during the reference period. Sixty-three cases were medically confirmed and 37 cases were medically unconfirmed. Twenty ADRs out of 215 were serious.

There were no reported cases of cataract/retinal degeneration/ retinal atrophy, phospholipidosis/fibrosis, neuroleptic malignant syndrome, cerebrovascular disease, sexual dysfunction, prolactin increased, liver enzyme increased, or sudden death/QT prolonged. No new relevant safety issue was identified from the available post-marketing reports.

2.7.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The most frequent treatment-emergent adverse events included akathisia (14.8%) / extrapyramidal disorder (7.3%), headache (12.5%) and insomnia (13.9%). The most frequent SAEs and AEs leading to premature discontinuation were worsening of schizophrenia, psychotic symptoms followed by akathisia. Several AEs including akathisia / restlessness, CPK elevation, insomnia, anxiety and blurred vision were dose-dependent.

Extrapyramidal symptoms, dominated by akathisia were among the most frequent TAEs in the cariprazine development program. Comparing the modal doses in short-term studies, akathisia was observed with 9% incidence in 1.5-3 mg and with 13% in the 4.5-6 mg cariprazine groups while 9% in risperidone 4mg and 7% in aripiprazole 10 mg. When akathisia/restlessness grouped the incidences are 12% in 1.5-3 mg, 18% in 4.5-6 mg cariprazine, 10 % in risperidone 4mg and 11% in aripiprazole groups. Thus, the incidence of akathisia was higher with cariprazine doses above 3 mg relative to the active comparators.

The high incidence of akathisia in clinical practise could result in compromised treatment adherence as it generally occurs during the first weeks after initiation. Moreover, although not observed in the cariprazine development program, akathisia has been reported in the literature to be associated with tendency for suicidality. However, none of the patients who died due to completed suicide during the cariprazine clinical development program had high akathisia scores. The safe use of the product in the context of early detection and mitigation of treatment emergent akathisia /restlessness, and prevention of suicide should be assured by individualized dosing regimen with close monitoring during the initiation of the treatment and lowest effective maintenance doses.

Based on pre-clinical finding of ocular toxicity, ophthalmological tests were performed in long-term schizophrenia studies. Positive lenticular shifts from Grade I to III have been observed in LOC III examinations in long-term studies and 24 cataract cases were reported in the overall cariprazine program of which 6 were within the schizophrenia program and had relatively young mean age. Moreover, up to

7% of the cariprazine treated patients had reduced visual acuity (BCVA changes ⩾ 0.3). The duration of long–term safety studies were limited to maximum 48 weeks which might not correspond to a sufficient duration in order to detect cataractogenic changes. The studies where ocular examinations were performed had different length and design. The exposure of to cariprazine differed in these studies and a tolerability based bias for study continuation should be taken into account for the long-term open-label studies (Group 1B). The preclinical findings in dogs were attributed by the Applicant to decreased cholesterol levels; however, this is not a relevant mechanism for humans as decrease in cholesterol was not observed in patients. Several of the cataract cases had relevant confounding risk factors for the cataract including concomitant drugs, prior treatments with known cataract risk or comorbidities such as diabetes. Although the causality between cataract cases and cariprazine treatment is not completely clear, the lenticular changes observed in the cariprazine program need to be further evaluated. Consequently, the Applicant committed to conducting a Post Authorisation Safety Study to characterise the ocular safety.

Elevations in blood pressure were reported in cariprazine treated patients. The frequency of hypertension related TEAEs were 2.6% in the claimed cariprazine posology, 1% for the placebo. Hypertension was mainly considered as mild to moderate; 4 patients had severe hypertension and 3 patients discontinued due to these AEs. Shifts from normotensive to stage I or II hypertension were reported in all dose groups up to 3.3 % in short-term Group 1A studies, and up to 14.8% in long-term studies for the claimed cariprazine posology of 1.5-6 mg/day; 6.6 % in Group 1A to 8% in long-term studies for placebo, 0 in short-term studies and 3.8% in long-term studies for risperidone; 3.5% in short-term studies for aripiprazole. The potential impact of blood pressure elevations and metabolic effects were discussed in terms of long-term cardiovascular safety of patients. Hypertension is listed as a common adverse event in the product information with a warning text for caution in patients with known cardiovascular disease predisposing to blood pressure changes and need for monitoring.

Increased CPK TEAEs were reported with frequency of 2.6% in the cariprazine and 1.6% in placebo groups. Although reported TEAEs and SAEs were not as frequent in relation to the higher rate of potentially clinically significant increases in CPK, a potential risk for rhabdomyolysis is suspected due to the class effect. Therefore, rhabdomyolysis is classified as an important potential risk for cariprazine.

Increased liver aminotransferases (ALT/AST) were reported for cariprazine with a frequency of 2.2% in the claimed posology for the grouped TEAEs and 0.4 % in the placebo. One patient has SAE of hepatitis, none met the Hy's law criteria, 5 patients discontinued their treatment due to abnormalities in liver enzymes. The risk for transaminase elevations and the need for monitoring is therefore reflected in the product information.

As cariprazine is a blocker of the serotonin 5HT2C, an increase in appetite and weight and related metabolic changes are expected. Both in short- and long-term studies, clinically relevant increases in body weight (⩾7%, in 6-28%), total cholesterol (> 1.3 × ULN, in 4-7%) and LDL cholesterol (> 1.2 × ULN, in 8-26%), triglycerides (>1.2 × ULN, in 5-27%) and fasting glucose (>1.2 × ULN, 5-13%) has been observed with cariprazine. Potential clinically relevant weight gain (⩾7%) was observed in 7.4% of cariprazine treated, 16.4% of risperidone and 6% of aripiprazole treated patients in short term studies, in 28% of cariprazine treated patients in group IB studies, as well as in 9.0% in cariprazine treated patients during the open-label phase and in 7.1% of placebo treated and 9.8% of cariprazine treated patients during the double-blind phase of the RGH-MD-06 study, and in 6% of cariprazine and 7.4% of risperidone in the long-term RGH-188-005 study. This indicates that although an initial difference was observed in terms of weight gain, with longer exposure no major differences would be expected between the two drugs in terms of weight gain or metabolic parameters. Weight gain is a common risk with second

generation antipsychotics and due to the high frequency of potentially clinically significant weight gain (≥ 7%) was observed and reported especially in the long-term studies in the cariprazine program it was recommended that weight gain is separated from other metabolic changes and classified as important identified risk in RMP.

No major differences in metabolic parameters or blood pressure shifts from normotensive to stage I or II hypertension were observed between risperidone and cariprazine. During the schizophrenia studies patients with any cardiovascular disease that was clinically significant, unstable, or decompensated were excluded. However, most patients were overweight with a mean BMI ⩾ 26 kg/m2. Patients with schizophrenia are known to have an increased risk for cerebro- and cardiovascular disorders. This is further aggravated by an increased cardiovascular risk from antipsychotic treatment. Based on the data available, it seems that this risk is similar for cariprazine and other second generation antipsychotics as risperidone. Moreover, considering the dose-dependency of changes in above mentioned variables it is of importance that the lowest effective maintenance dose is chosen. In summary, increased blood pressure, metabolic changes including dyslipidemia and dysregulation of glucose and weight gain are known class effects for atypical antipsychotics. Warnings concerning the metabolic changes, blood pressure alterations and their potential consequences are reflected in the product information.

In general, there were only minor elevations within the reference ranges of prolactin levels observed in cariprazine-treated patients in the clinical studies and no AE of hyperprolactinemia was reported. Mean decreases in prolactin levels from baseline were seen in all treatment groups, with the exception of the risperidone group. Moreover, decreased prolactin levels were more pronounced in women compared to men in clinical short-term and open-label studies, whereas prolactin elevations were observed in female rats. The prolactin decrease observed in patients with schizophrenia and mania (where first line treatments include antipsychotics) were highly probable due to the cessation of the previously taken antipsychotic, which potentially caused prolactin increase, and normalizing during cariprazine treatment.

In the cariprazine schizophrenia program cognition related TEAEs were reported in 1.0% of patients in the claimed posology which was similar to placebo and risperidone. Moreover, an improvement in PANSS based cognitive subscale was shown for cariprazine both in short-term and long-term studies.

The effect of cariprazine on the ability to drive or to operate machinery was not systematically evaluated in the clinical development program. However since cariprazine causes e.g. akathisia and restlessness it can be assumed that it has some effects on the ability to drive or to operate machinery.

Pre-clinical toxicity showed that phospholipidosis occurred in the lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal gland cortex of dogs at clinically relevant exposures (AUC) of total cariprazine. In the clinical program no AE potentially related to phospholipidosis was detected in form of lung inflammation or adrenal hyperplasia/hyperthropia. Concerning adrenal insufficiency, a substantial frequency of clinically relevant weight loss has been observed in especially in long-term schizophrenia studies. However, no patient with potentially clinically significant weight increase or decrease experienced more than one TEAE indicative of adrenal hypofunction at the same time or multiple symptoms that would point into the direction of adrenal malfunction.

Cariprazine is a teratogenic substance as evidence by the non-clinical findings. As pregnant women were excluded in clinical trials, limited data is available on the effects of cariprazine on the reproduction of humans. As there are uncertainties concerning potential pharmacokinetic interactions between oral contraceptives and cariprazine, the applicant should discuss suitable methods for contraception that should be advised to patients. In addition a DDI study with oral contraceptives has been requested by the

CHMP.

2.7.2. Conclusions on the clinical safety

The safety concerns, including EPS/akathisia, weight changes, ocular changes and other treatment emergent adverse events are reflected in the product information and the safety specification.

The CHMP considers the following measures necessary to address issues related to safety:

The Applicant will conduct a Post Authorisation Safety Study to further characterise the risk of cataract development.

2.8. Risk Management Plan

Table 44. Summary of the Safety concerns

Important identified risks	Extrapyramidal symptoms including tardive dyskinesia Weight gain
Important potential risks	Neuroleptic Malignant Syndrome Metabolic changes (Hyperglycaemia, dyslipidaemia) Ocular changes (lenticular changes and cataracts) Suicidal ideation and behaviour Rhabdomyolysis Interaction with CYP3A4 inhibitors and inducers Developmental and reproductive toxicity
Missing information	Use during lactation Use in patients >65 years Use in patients with severe renal or hepatic impairment

Pharmacovigilance plan

Table 45. Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Clinical study to investigate the effect of cariprazine on the pharmacokinetics of combined oral contraceptive (Ethinyl Estradiol and Levonorgestrel) (category 3)	Confirm that cariprazine has no clinically meaningful effect on the pharmacokinetics of the selected COC.	Interaction with CYP3A4 inhibitors and inducers	Planned	CSR: Q1 2021
Clinical study to investigate the interaction between cariprazine and a moderate CYP3A4 inhibitor (erythromycin) in patients with different CYP2D6 genotypes (category 3)	Provide dosing recommendations when cariprazine is used concomitantly with moderate CYP3A4 inhibitors. Investigate the effect of different CYP2D6 genotypes on the exposure of cariprazine.	Interaction with CYP3A4 inhibitors and inducers	Planned	CSR: Q3 2020
Post-authorisation safety study (PASS) - A randomized, open-label, ophthalmologist-masked study in approximately 1000 schizophrenic patients to compare lens opacity changes during long-term treatment with cariprazine versus risperidone. The study duration will be 2 years and special lens opacity scale such as the modified Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System for classifying cataracts will be applied	Proposed PASS will focus on the long-term effects and the reversibility of the symptoms upon withdrawal of the drug.	Ocular adverse events (lenticular changes and cataract)	Planned	Submission of the protocol for PRAC review and endorsement with 3 months from the EC decision CSR - Q4 2024

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
(category 3)				
In vitro metabolism studies of DDCAR to explore contribution of unusual CYP (CYP2C8, CYP2J2) and other oxidative enzymes (category 3)	Identifying further (not so common) enzymes in the metabolism of DDCAR	Not Applicable DDCAR is metabolised mainly via CYP3A4, however uncommon CYP enzymes and other oxidative enzymes may pay a role in the elimination. No safety concern is raised.	Planned	CSR - Q3 2018

Risk Minimisation Measures

Table 46. Summary table of the Risk Minimisation Measures

Safety concern	Routine RMMs	Additional RMMs
Important identified risks		
Extrapyramidal symptoms including tardive dyskinesia	Wording in SmPC section 4.4, 4.6, 4.8 Prescription only medicine	None
Weight gain	Wording in SmPC section 4.4, 4.8 Prescription only medicine	None
Important potential risks		
Neuroleptic malignant syndrome	Wording in SmPC section 4.4, 4.8 Prescription only medicine	None
Metabolic changes (Hyperglycaemia, Dyslipidaemia)	Wording in SmPC section 4.4, 4.8 Prescription only medicine	None
Ocular changes (lenticular changes and cataracts)	Wording in SmPC section 4.4, 4.8, 5.3 Prescription only medicine	None
Suicidal ideation and behaviour	Wording in SmPC section 4.4, 4.8 Prescription only medicine	None
Rhabdomyolysis	Wording in SmPC section 4.4, 4.8 Prescription only medicine	None

Safety concern	Routine RMMs	Additional RMMs
Interaction with CYP3A4 inhibitors and inducers	Wording in SmPC section 4.3, 4.5 Prescription only medicine	None
Developmental and reproductive toxicity	Wording in SmPC section 4.4, 4.5, 4.6 and 5.3) Prescription only medicine	None
Missing information		
Use during lactation	Wording in SmPC section 4.6, 5.3 Prescription only medicine	None
Use in patients >65 years	Wording in SmPC section 4.2, 4.4 Prescription only medicine	None
Use in patients with severe renal or hepatic impairment	Wording in SmPC section 4.2, 5.2 Prescription only medicine	None

Conclusion

The CHMP and PRAC considered that the RMP version 1.5 (dated 17 May 2017) is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 06.10.2004. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. New Active Substance

The applicant compared the structure of cariprazine with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers cariprazine to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Quick Response (QR) code

A request to include a QR code in the package leaflet has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: Package Leaflet

2.11.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Reagila (cariprazine) is included in the additional monitoring list as it contains new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Schizophrenia is one of the most frequent and debilitating psychotic disorders with worldwide lifetime morbidity risk of about 1 percent. The age of onset of the first psychotic episode is typically in the late teens, but can be as late as into the mid-thirties. Onset prior to adolescence is rare.

The symptoms of schizophrenia are classified as positive (delusions, hallucinations, disorganised speech, and disorganised or catatonic behaviours) and negative (affective flattening, restriction in the fluency and productivity of thought and speech and in the initiation of goal directed behaviour). In addition, cognitive deficits are common. The positive symptoms appear to reflect an excess or distortion of normal functions, whereas negative symptoms reflect a diminution or loss of normal function.

Primary negative symptoms are outstanding and insistent in up to a quarter of the patients with schizophrenia, and approximately half of the first-episode acute schizophrenia and up to two thirds of all chronic outpatients might experience negative symptoms at any given time.

3.1.2. Available therapies and unmet medical need

Despite the available treatments, there is a substantial unmet medical need especially for treatment of negative symptoms which affect up to two thirds of the patients with schizophrenia. To date, no standard treatment has been established for negative symptoms. Of the available treatments for schizophrenia, clozapine, amisulpride, olanzapine, and risperidone have shown modest efficacy on negative symptoms. The hypothetical expectation of cariprazine's benefits in treatment of schizophrenia including the predominant negative symptoms has been based on its receptor profile with partial agonism and preferential binding to dopamine D3 receptors in addition to D2 and serotonin 5-HT1A receptors.

3.1.3. Main clinical studies

The efficacy of cariprazine was documented in five pivotal trials, three short-term trials, one long-term, maintenance of effect study, and a long-term study in patients with predominant negative symptoms of schizophrenia. The sort-term trials (RGH-MD-16, RGH-MD-04, and RGH-MD-05) were 6-week,

double-blind, placebo- and active-controlled, with fixed or fixed/flexible doses of cariprazine in the range 1.5-9 mg/day, performed in in adult patients with acute exacerbation of schizophrenia at European, US and other study centers. The active controls were 10 mg aripiprazole and 4 mg risperidone (in study RGH-MD-04 and GH-MD-16, respectively).

The long-term maintenance of effect study, (RGH-MD-06), was a double-blind, placebo-controlled, randomized-withdrawal study in order to assess prevention of relapse, with fixed cariprazine doses of 3 mg/day to 9 mg/day, for 20 weeks (open-label phase), followed by a placebo-controlled double-blind phase of 26 weeks. Patients came from European countries (Ukraine, Slovakia, Romania), India and the US.

The long-term study in patients with predominant negative symptoms of schizophrenia (RGH-188-005) had a randomized, 26-week, double-blind, risperidone controlled design in patients with predominant negative symptoms, treated with fixed/flexible cariprazine doses of 3 to 6 mg/day, with a target dose of 4.5mg/day. All patients were from Europe.

3.2. Favourable effects

The short-term efficacy of cariprazine in acute exacerbation of schizophrenia has been measured as improvement primarily in PANSS total score supported by CGI-S scores for the dose range of 1.5-6 mg/day and was comparable to that of aripiprazole whereas slightly smaller than that of risperidone.

A dose-dependent decrease in the PANSS total score has been observed in acute schizophrenia patients treated with fixed doses of 1.5, 3 and 4.5 mg/day cariprazine and the active control of 4 mg/day risperidone after 6 weeks of double-blind treatment in study RGH-MD-16. The LSMD (p-value) for 1.5 mg/day cariprazine was –7.5 ($p = 0.0005$); for 3 mg/day, –8.8 ($p<0.0001$); for 4.5 mg/day –10.4 ($p < 0.0001$) and for risperidone -15 ($p<0.0001$) (LOCF analysis). The PANSS responder status (≥30% decrease from baseline) was achieved in all cariprazine dose groups and risperidone treated patients with 31% ($p=0.015$), 36% ($p=0.002$), 36% ($p=0.001$) and 44% ($p<0.001$) in 1.5, 3, and 4.5 mg/day cariprazine and risperidone, respectively. The secondary endpoint, CGI-S, also showed statistical significance over placebo in all dose groups (LOCF).

The efficacy of fixed doses 3 and 6 mg/day cariprazine has been shown in study RGH-MD-04 in acute schizophrenia patients as the change in PANSS total score was statistically significant over placebo after 6-weeks double-blind treatment with 6 mg/day cariprazine (LSMD –8.8, $p<0.0001$) and 3 mg/day (LSMD –6.0, $p=0.0044$) and with the active-control aripiprazole 10 mg (LSMD -7.0 , $p=0.0008$) (MMRM, confirmed with LOCF analysis). On the other hand, the responder rates (PANSS≥30%) differed from placebo only for the 6 mg/day cariprazine (responder rate, 20% for placebo, 25% for 3 mg/day ($p=0.28$), 32% for 6 mg/day ($p=0.027$) and 30% for aripiprazole ($p=0.0313$)). The results for the secondary end-point CGI-S were statistically significant for all the treatment groups both with MMRM and LOCF analysis.

Statistically significant decreases in PANSS total score were also observed in study RGH-MD-05 in acute schizophrenia patients with cariprazine modal doses of 3-6 and 6-9 mg/day, evaluated with a fixed/flexible-dose design, titrating patients to the higher doses within groups based on response. The LSMD compared to placebo was –9.9 ($p<0.0001$) for 6 to 9 mg/day group, -6.8 ($p=0.0029$) for 3 to 6 mg/day group (MMRM, confirmed with LOCF analysis). The responder rates (PANSS≥30%) did not differ from placebo for any of the dose groups (placebo (25%), 3-6 mg (29%, $p=0.485$), 6-9 mg (35%, $p=0.07$)). The secondary endpoint, change in the CGI-S was statistically significant in both dose groups compared to placebo. Doses > 6 mg cariprazine are not covered by the proposed posology.

The maintenance of effect has been shown with relapse-prevention in RGH-MD-06. Patients were stabilized on cariprazine during 20 weeks of open-label, flexible dose, 3-9 mg cariprazine treatment phase of the study, and during the following 26-week double-blind phase of the study, 48% of placebo-treated patients, 25% of patients treated with 3 to 9 mg of cariprazine have met predefined relapse criteria (p=0.001, hazard ratio [95% CI]; 0.45 [0.28, 0.73]). The 25th percentile for time to relapse was 92 days in the placebo group and 224 days in the cariprazine group. The post-hoc results excluding the >6mg doses were similar.

Cariprazine's effects on negative symptoms were evaluated in study RGH-188-005, in patients with predominant negative symptoms of schizophrenia. The dose range of 3-6 mg/day cariprazine was reported to show a statistically significant better improvement in favour of cariprazine over risperidone at the end of week 26 (p= 0.002). The LS mean change from baseline at week 26 was -8.9 and -7.4 for cariprazine and risperidone, respectively. The pairwise difference was -1.5 (95% CI: -2.4, -0.5). The secondary efficacy parameter was the change from baseline to week 26 in the PSP score analysed with MMRM and the LSMD for cariprazine was 14.3 and for risperidone was 9.7 (p<0.001). Cariprazine decreased the Personal and Social Performance (PSP) total score by 14.3 points compared to 9.7 points by risperidone at week 26 (p<0.001); the pairwise difference was 4.6 (95% CI: 2.7, 6.6).

3.3. Uncertainties and limitations about favourable effects

Only a small portion of patients in the schizophrenia development programme came from the EU. Large differences in the change of PANSS between geographical areas (i.e. European and non-European) in short-term studies RGH-MD-04 and RGH-MD-16 were observed. This is of importance when evaluating efficacy and other possible differences between areas and when extrapolating foreign data to the European population. The Applicant has appropriately described and discussed the suitability of extrapolation of results from clinical studies conducted outside the EU in relation to similarities in standard medical care within EU region.

In short-term there appears to be evidence of dose-response, though in long-term maintenance evidence of dose-response or optimal dose is not clear. Efficacy of cariprazine dose 1.5 mg/day in prevention of relapse has not formally been studied. The very limited data of long-term exposure for the 1.5 mg/day is generated from 7 patients in study RGH-MD-17 open-label study. The effect was maintained in these patients. The exposure-response model (PANSS vs concentration of active moiety (cariprazine + DCAR + DDCAR) suggests that 3 mg to 4.5 mg is efficacious in the treatment of schizophrenia and that the incremental benefit of higher doses is limited. Instead, the risk of treatment related adverse events (akathisia, EPS) increases with increasing concentration. The results from PET studies show that 1.5 mg to 3 mg cariprazine provides approximately 80% D2 occupancy and 90% D3 occupancy. This indicates that dose levels < 3mg may be sufficient for pharmacological response provided that pharmacokinetic steady state is reached. The time to achieve pharmacokinetic steady state is long, in the order of one month for the total active moiety. Specifically the important active metabolite DDCAR accumulates slowly. This implies that clinical efficacy as well as side effects would take long time to develop and may be difficult to manage. Based on the totality of the data it can be concluded that dose dependency for response is established for the claimed posology 1.5-6mg/day. On the other hand, taking into account the dose-dependent adverse events, up-titration and maintenance dose can be adjusted according to the clinical judgement of the treating physician and lowest effective dose achieving relapse prevention should be maintained.

There is no adequate PK or efficacy data concerning use in elderly patients suffering from schizophrenia and within claimed posology. Only 17 elderly patients using cariprazine with doses 1.5-9 mg/day were included into the Japanese study A002-A7; among elderly discontinuation rate due to adverse events was almost 50%. No studies in elderly EU population have been conducted. The clinical studies did not enrol

subjects with an age above 60 years with the exception of the study on negative symptoms, RGH-188-005. However, the applicant used data from the RGH-188-005 study to perform an extrapolation from the efficacy at younger ages to elderly patients. A regression approach in order to examine whether there was a decline in efficacy with increasing age revealed that there was no significant decline in efficacy in terms of PANSS-FSNS with increasing age. Overall, it is agreed that the efficacy data of cariprazine in older adults does not seem to change when compared to the younger adults. Thus, efficacy results from younger adults can be broadly extrapolated to the older adults. However, the uncertainties regarding dose recommendation and safety are still remaining and were reflected in the SmPC.

Concerning the treatment of patients with predominant negative symptoms in adult patients, one pivotal study was provided; RGH-188-005. Improvement in negative symptoms was shown both for cariprazine and risperidone and also supported by the improvement in personal and social performance of patients. In this study, the improvements for negative symptoms and personal and social performance were numerically and statistically better for cariprazine treated patients compared to the risperidone group. However, the clinical relevance of the difference in results between cariprazine over risperidone is difficult to interpret. In the short-term studies, in addition to assessment of positive symptoms, rating of negative symptoms was performed with the NSA-16 scale. However, the duration of the study, the acute treatment setting and the study population were not appropriate for evaluation of negative symptoms. Thus, the results regarding the negative symptom improvement from the short-term studies are only informative and no robust conclusions should be drawn based on these results.

3.4. Unfavourable effects

The unfavourable effects of cariprazine are comparable to those of other atypical antipsychotics. In the clinical schizophrenia studies, up to 81.7% of cariprazine treated patients treated with 1.5-6 mg /day had TEAEs, 6.6% had SAEs, 12.1% discontinued their treatment due to adverse events and there were 3 deaths. The most frequent AEs were akathisia (14.6%), insomnia (14.0%), and headache (12.1%). Other common AEs were restlessness (6.2%), weight increase (5.1%), dizziness (4.5%), and CPK increase (2.6%).

Based on pre-clinical finding of ocular toxicity, ophthalmological tests were performed in both short-term and long-term schizophrenia studies. Twenty-four cataract cases were reported in the overall cariprazine development program of which 14 has been reported as related to cariprazine treatment by the investigators (14/6120=0.22%) and 1 cataract was reported related to placebo (1/1820=0.06%). Six of these cataract cases were observed in the schizophrenia program among cariprazine treated subjects (6/2728=0.22%). However, due to several confounding risks of the cases, the causality between cariprazine treatment and cataract cannot be concluded.

Extrapyramidal symptoms, dominated by akathisia, were among the most frequent TAEs in the cariprazine development program (14.6% in the claimed posology and 3.4% in placebo). Akathisia was mostly reported within the initial 5-6 weeks of the cariprazine treatment, however, longer time to onset was observed up to week 36 in the long-term studies and with the majority judged as mild to moderate in severity. Akathisia was mainly managed with anti-EPS medications (propranolol, benztropine and trihexyphenidyl) in cariprazine treated patients while with dose reductions in risperidone treated patients during the comparison studies. Time to resolution of EPS-related TEAEs tended to be shorter with lower doses of cariprazine (measured by days to resolve 50th percentile around 14 days for 1.5 mg, up to 43 days for 6 mg). Akathisia was the second most frequent adverse event (following exacerbation of underlying disease) that led to treatment discontinuation both in short-term Group 1A (0.5%) and long-term Group 1B studies (0.7%), open-label phase of the RGH-06 maintenance of the effect study (1%) and RGH-188-005 negative symptom study (3%).

Clinically significant elevations in blood pressure and TAEs of hypertension were reported with low incidences in all studies (2.6% related to cariprazine, 1.6% in risperidone, 0.7% in aripiprazole and 1% in placebo). In patients treated with the highest doses of cariprazine dose range 1.5-6 mg/day, mean elevations in SBP up to 1.9 mmHg and DBP elevations occurred up to 0.9 mmHg with large standard deviations suggesting a skewed distribution. Shifts from normotensive status at baseline to stage I or II hypertension were reported in all dose groups up to 3.3% of patients in short-term Group 1A studies, and up to 14.8% in long-term studies. The risk of hypertension is reflected in the product information together with other class effects.

Elevations of creatinine phosphokinase (CPK) were dose-dependent. Although low frequency for TAEs was reported (2.6% within the cariprazine claimed posology and 1.6% in placebo groups) due to the risk of the class, rhabdomyolysis is included in the safety specification.

No cariprazine-induced serious liver injury was reported during the cariprazine clinical program but increased liver aminotransferases were observed.

Unfavourable metabolic changes with cariprazine use may be less harmful than with some other atypical antipsychotics (such as risperidone), however; increases in blood glucose, cases with diabetes mellitus were observed; dyslipidaemias (including hypertriglyceridaemia, hypercholesterolaemia and hyperlipidaemia) are common ADRs.

Increased body weight and weight loss were reported in cariprazine treated patients. Potentially clinical significant weight gain increased (≥7%) was observed up to28% of cariprazine treated patients while weight loss (≥7%) has also been observed in up to 12% of patients in long-term studies.

Sedation related TEAEs were reported up to 7.5 % in overall cariprazine treated patients and were similar between the risperidone and cariprazine treated patients in RGH-188-05 negative symptom study, 5.2% and 6.0%, in cariprazine and risperidone treated patient, respectively.

3.5. Uncertainties and limitations about unfavourable effects

The applicant has submitted a large amount of safety data, which appear to be representative of the target population and sufficient to support the use of the product. Exceptions are the elderly and patients with severe renal or hepatic impairment who were not included in the European/US studies and are thus currently "missing information". Only 50 patients aged 65-74 and no patient above the age of 74 received cariprazine during the development program; of these only three (not older than 65) were enrolled to the main clinical schizophrenia studies. Thus, only limited data exists on the safety of cariprazine in the elderly schizophrenic population. The Applicant has proposed to gather relevant data on elderly patients with a targeted follow up questionnaire post approval.

With regards to long-term use, 508 patients were exposed to the cariprazine claimed posology for the duration of 24 weeks and 225 patients for 48 weeks. Moreover, 122 cariprazine treated patients in the claimed posology were exposed more than 12 months. At this point, there remains a concern that cariprazine may cause late developing AEs such as ocular adverse events (lenticular changes and eventually cataracts).

The causality between cataract cases and cariprazine treatment is not clear due to confounding risk factors. However, the dose-dependent blurred vision and observed lenticular changes in ocular assessments in long-term studies, reversibility of the few cataract cases after discontinuation of cariprazine warrants further evaluation of this risk. The Applicant has proposed routine risk minimisation measures in terms of a targeted adverse event form for ocular adverse events, and updated the product information with findings on lenticular changes from the clinical development program. Moreover, a PASS has also been agreed in order to further characterise this safety concern.

Reproductive adverse findings in rats (both teratogenic effects in the developmental toxicity study, as well as adverse effects in the F1-generaiton and unusual adverse findings in F2-generation observed in the peri-postnatal study) raises serious concerns regarding exposure in pregnancy as well as of women of child bearing potential. For the intended target population, this potential important risk may be particularly challenging to handle in clinical use. This is evident by the fact that despite strict recommendations to avoid becoming pregnant, 22 pregnancies occurred during the clinical program. Based on the non-clinical findings, reproductive toxicity was included as an important potential risk in the RMP. Reagila is not recommended during pregnancy or in women of child-bearing potential not using highly effective contraception.

Akathisia and especially restlessness have been reported in the literature to be associated with suicidality. This association has been evaluated in cariprazine program and not confirmed. The high frequency of akathisia and restlessness during the initial weeks of the cariprazine treatment and the vulnerable patient population with acute exacerbation of schizophrenia are potential risk factors for suicidality. This should be considered in routine clinical practise where patients may not be as closely monitored as in the clinical trial setting.

From the clinical PK perspective, the most important uncertainties relate to interactions with CYP3A4 and CYP2D6 inhibitors. For various reasons, the ketoconazole (i.e., a strong CYP3A4 inhibitor) study may not have captured the full extent of CYP3A4 inhibition and the effect of moderate CYP3A4 inhibitors on PK of cariprazine and its active metabolites is unknown. Additionally, exposure to cariprazine and metabolites could increase to unexpectedly high levels if activity of both CYP3A4 and CYP2D6 was impaired or inhibited, for example, by interactions and/or genetic factors. This is also a potential risk that remains to be clarified.

Effects Table

Effects Table for Reagila for the treatment of adults with schizophrenia (data cut-off: Nov 2015).

Effect	Short Description	Unit	CAR	PBO	RISP	ARI	Uncertainties/ Strength of evidence	References
Favourable Effects								
			1.5 mg -7.5 (-11.8,-3.3) 3mg -8.8 (-13.1, -4.6) 4.5 mg -10.4 (-14.6, -6.2)		4 mg -15 (-19.4, -10.8)		p=0.0005, p<0.0001 p<0.0001 for 4.5 mg car and 4 mg risp	E1
Improvement in in acute exacerbation of schizophrenia	PANSS Change from baseline at week 6	LSMD vs placebo (95%CI)	3mg -6 (-10.1—1.9) 6mg -8.8 (-12.9, -4.7)			10 mg -7.0 (-11, -2.9)	p=0.004 for 3 mg, p<0.0001 for 6 mg cariprazine P=0.0008 for aripiprazole	E2
			3-6 mg -6.8 (-11.3, -2.4) 6-9 mg-9.9 (-14.5, -5.3)				P=0.0029 for 3-6 mg car, <0.0001 for 6-0mg car	E3
Maintenance of effect/ Relapse prevention	Relapse rate at week 26	%	25	48			p=0.001, hazard ratio and 95% CI, 0.45 [0.28, 0.73]	E4
	25th percentile for time to relapse	Days	224	92			p = 0.001	

Effect	Short Description	Unit	CAR	PBO	RISP	ARI	Uncertainties/ Strength of evidence	References
Improvement in Negative Symptoms	Change in PANSS Negative Symptom score from baseline at 26 weeks	LSMD vs risperidone (95% CI)	-8.9		-7.4		P = 0.002 for -1.5 difference for cariprazine versus risperidone	E5
Improvement in personal and social performance	Improvement in PSP scale from baseline to week 26	LSMD Vs risperidone	14.3		9.7		P<0.001 for 4.6 difference for cariprazine versus risperidone	
Unfavourable Effects								
Akathisia	Incidence of akathisia in 6-week short-term studies (Group 1A)	%	11.3	3.6	8.6	7.2	Reflects the initial treatment duration that is relevant for highest akathisia onset	s1
Blood pressure elevations	Incidence of shifts from normotensive to hypertension Stage I or II	%	2-7 15-22 0-5 OL/0-14 DB 0-2.4	2.4 4	0 4	3.5	Open-label 48 week studies lacking placebo or active controls	s1 s2 s3 s4

Effect	Short Description	Unit	CAR	PBO	RISP	ARI	Uncertainties/ Strength of evidence	References
CPK elevations	Incidence >1.5 x ULN >1000 U/L >5000U/L >1.5 x ULN >1000 U/L >5000 U/L	%	 23 5 0.2 36 9 1.2	 14 3.5 0	 23 4.5 0	 19 2 0.7	Initial effects of 6 weeks 48-week data follow-up	s1 s2
Elevation of liver aminotransferase	Incidence ≥ 3 × ULN ≥ 5 × ULN ≥ 5 × ULN	%	 3OL 5DB 0.7OL 1 DB 0OL 1DB	 0 0 0			48 week follow-up	s2
Cataract	Number of patients	n	24 patients of whom 14 related TEAE	1			Confounding factors (questionable), 48 week exposure may not be long enough for cataract development	s5
Body weight increase	Incidence of ≥7% increase	%	9 27 11OL 27DB 6	5 32	17 7.4	6		s1 s2 s3 s4
Body weight decrease	Incidence of ≥ 7% decrease		1.5 11 4OL 12DB 12	3.1 13	0.7 6	1.3		s1 s2 s3 s4

Effect	Short Description	Unit	CAR	PBO	RISP	ARI	Uncertainties/ Strength of evidence	References
Sedation related TEAEs	Incidence	%	7.5 7.1 5.2OL 3DB 5.2	6 0 	 6		The time of administration of the drug needs to be clarified	s1 s2 s3 s4

Abbreviations: CAR: Cariprazine, PBO:Placebo, RISP: Risperidone, ARI: Aripiprazole LD: low dose 1.5-3 mg, MD: medium dose 4.5-6 mg, HD: High dose, 9-12 mg, OL: Open-label, DB:Double-blind

Notes:

E1: RGH-MD-16 study, 6-week active- and placebo-controlled study in schizophrenia patients

E2: RGH-MD-04 study, 6-week active- and placebo-controlled study in schizophrenia patients

E3: RGH-MD-05 study, 6-week placebo-controlled study in schizophrenia patients

E4:RGH-MD-06 maintenance of effect study,

E5: RGH-188-006 negative symptom study,

s1: Group 1A, 6-week active- or placebo-controlled studies in schizophrenia patients,

s2: Group 1B, 48 week, Open-label follow-up studies (RGH-MD-11 and RGH-MD-17),

s3: RGH-MD-06, Maintenance of effect study,

s4: RGH-188-005, Negative symptom study,

s5: The total safety population including all indications (schizophrenia, bipolar mania, major depressive disorder and PK/PD studies.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The results of the short-term studies have shown clinically relevant effect of cariprazine in the treatment of psychotic symptoms of schizophrenia. Maintenance of effect in long-term use was confirmed in the randomised withdrawal study.

The pharmacological treatment for the positive symptoms of schizophrenia has progressed with introduction of atypical antipsychotics. However, no standard treatment exists for negative symptoms. Bearing in mind that the negative symptoms have a great impact on functional disability, decreased quality of life, increased burden of illness and poor treatment outcome, any advance in treatment of such symptoms would be of substantial value. The study RGH-188-005 was designed to evaluate the effect on negative symptoms and has shown significant symptom improvement for both cariprazine and risperidone groups. Moreover, a statistically significant difference between cariprazine and risperidone was shown for both the improvement in negative symptoms and in PSP score, but the clinical relevance of the differences is difficult to interpret.

Most of the observed AEs are expected to be familiar to the practising clinicians and many of them are treatable. The exceptions, *i.e.* potential AEs that are not commonly expected with antipsychotics, are cataracts and the unlikely development of adrenal gland disorders. Again, both of these would also be treatable but suspicion and thus diagnostics of them may not be a trivial issue in patients with schizophrenia.

Positive lenticular shifts (suggesting worsening) have been observed in LOCS III examinations in long-term studies and supporting evidence by reductions of visual acuity have been reported. The reversibility of lenticular changes have been discussed further and proved inconclusive based on the provided data. The risk for lenticular changes and cataracts will be studied further in a post approval safety study and several risk minimization measures are agreed which are considered acceptable based on the existing knowledge for this risk.

Considering class-related adverse events, the incidence of akathisia was somewhat higher for cariprazine compared to risperidone and aripiprazole in the comparative studies. This could possibly influence treatment adherence, but could most likely be handled in clinical practice with anti-EPS medication.

Akathisia typically occurs during the initial weeks of the treatment and tends to require several weeks to resolve. This may substantially influence the adherence to treatment. Data from schizophrenia studies in the cariprazine program show that most of the study discontinuations were due to exacerbation of underlying disease and akathisia. Therefore, individual up-titration based on the observed effect and tolerance as well as the lowest effective maintenance dose according to the judgement of the treating physician is recommended.

No elevation of prolactin levels was observed in cariprazine-treated patients in the clinical schizophrenia studies and no AEs of hyperprolactinemia were reported either. Thus, hyperprolactinemia and prolactin-associated signs and symptoms such as galactorrhoea, amenorrhea and gynecomastia in men do not seem to be a similar problem with cariprazine as with several other antipsychotics. Additionally, the studies did not indicate a harmful effect of cariprazine on renal function.

The elimination of cariprazine was investigated to an acceptable level based on the data generated using the unlabelled mass balance data and performed DDI studies. Undoubtedly, with data from the unlabelled mass balance study only, there remains a lack of full understanding in the preclinical bridge regarding human metabolites although this uncertainty is considered low. In particular safety concerns related to reproductive toxicity, genotoxicity or carcinogenicity are not fully evaluated in the clinical program. As Reagila is not recommended during pregnancy or in women of child-bearing potential not using highly effective contraception, concerns related to reproductive toxicity are considered mitigated. In addition, it is also proposed that reproductive toxicity is included as an important potential risk in the RMP. Thus, the main safety concern of a potential unique human metabolite is related to genotoxicity and/or carcinogenicity. However, as cariprazine metabolites share the predominant structural moieties of the parent substance, and as neither cariprazine, nor its major human metabolites DCAR and DDCAR unveiled any mutagenic or carcinogenic potential, the risk may be regarded as low. Taken together, the available data indicate a low risk for the occurrence of a unique major human metabolite, and if present, a potential risk for a mutagenic or carcinogenic potential is also considered low. Therefore, given the risks associated with prolonged ocular human exposure to radiolabelled cariprazine, it was not considered justified to request further mass balance evaluation.

3.6.2. Balance of benefits and risks

The overall B/R of Reagila is positive.

Although initially the Applicant requested additional separate indication for the treatment of patients with predominant negative symptoms, the CHMP concluded that this is not warranted. This population is understood to be included in the general "schizophrenia in adults" indication, which covers both positive and negative symptoms.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Reagila is favourable in the following indication:

Treatment of schizophrenia in adult patients.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that cariprazine is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.