Cariprazine (VRAYLAR®) Met Primary Endpoint in Phase 3 Study as an Adjunctive Treatment for Major Depressive Disorder

- *In a Phase 3 clinical trial, Study 3111-301-001, cariprazine (VRAYLAR®) met its primary endpoint demonstrating statistically significant change from baseline to week six in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score in patients with major depressive disorder*
- In a second Phase 3 clinical trial, Study 3111-302-001, cariprazine demonstrated numerical improvement in depressive symptoms from baseline to week six in MADRS total score compared with placebo but did not achieve statistical significance
- Safety data were consistent with the established safety profile of cariprazine across indications with no new safety signals identified

Budapest, Hungary – 29 October 2021 – Richter's partner, AbbVie, today announced top-line results from two Phase 3 clinical trials, Study 3111-301-001 and Study 3111-302-001, evaluating the efficacy and safety of cariprazine (VRAYLAR®) as an adjunctive treatment for patients with major depressive disorder (MDD). In Study 3111-301-001, cariprazine showed a statistically significant change from baseline to week six in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared with placebo. Patients treated with cariprazine at 1.5 mg/day achieved improved MADRS total score at week six compared to placebo (p-value=0.0050). Patients treated with cariprazine at 3.0 mg/day demonstrated improvement in MADRS total score at week six over placebo but did not meet statistical significance (p-value=0.0727). In Study 3111-302-001, cariprazine demonstrated numerical improvement in depressive symptoms from baseline to week six in MADRS total score compared with placebo but did not meet its primary endpoint for either the 1.5 mg/day or 3.0 mg/day dose.

In a previously published Phase 2/3 registration-enabling study, RGH-MD-75, patients treated with cariprazine flexible doses of 2.0-4.5 mg/day in addition to ongoing antidepressant therapy (ADT) met the primary endpoint and achieved improved MADRS total scores at week eight compared to placebo (p-value=0.0114).

Based on the positive results of studies 3111-301-001 and RGH-MD-75, and the totality of data reported, AbbVie intends to submit a supplemental New Drug Application (sNDA) with the U.S. Food and Drug Administration for the expanded use of cariprazine for the adjunctive treatment of MDD.

"We are proud that a second Phase III clinical study showed statistically significant and clinically relevant improvement for a large group of patients not adequately responding to existing treatment" – said Mr Gábor Orbán, CEO of Richter. "These results get us one step closer to a potential new adjunctive treatment option for major depressive disorder."

The safety results of cariprazine in all three studies were consistent with its established safety profile across indications with no new safety signals identified. The most common adverse events occurring at ≥5% in the cariprazine groups during the six-week study period were akathisia, nausea, insomnia, headache and somnolence.

Full results from studies 3111-301-001 and 3111-302-001 will be presented at a future medical meeting.

MDD is a common condition with 19 million people of all ages affected in the United States.[1] The World Health Organization lists depression as the third-leading cause of disability worldwide and as a major contributor to the overall global burden of disease. Symptoms can include depressed mood, loss of pleasure or interest in activities, changes in appetite or weight, changes in sleep, psychomotor agitation, loss of energy, feelings of worthlessness, indecisiveness, and current thoughts of death.[2] In the United States, the mean age of onset for the first episode is 26 years old,[3] and MDD represents an estimated $211 billion economic burden.[4]

Cariprazine is marketed as VRAYLAR® in the United States and is FDA-approved to treat depressive, acute manic and mixed episodes associated with bipolar I disorder, as well as schizophrenia in adults. Cariprazine is being co-developed by Gedeon Richter Plc and AbbVie. More than 8,000 patients worldwide have been treated with cariprazine across more than 20 clinical trials evaluating the efficacy and safety of cariprazine for a broad range of psychiatric disorders.

About Studies 3111-301-001 and 3111-302-001
Study 3111-301-001 is a randomized, double-blind, placebo-controlled, multicenter trial with 759 participants conducted in United States, Bulgaria, Estonia, Germany, Hungary, Ukraine, and the United Kingdom. Study 311-302-001 is a randomized, double-blind, placebo-controlled, multicenter trial with 752 participants conducted in United States, Canada, Czech Republic, Finland, Poland, Serbia, and Slovakia. For both studies, following a screening period of up to 14 days, patients with an inadequate clinical response to their antidepressant monotherapy (ADT) were randomized into three treatment groups (1:1:1). The first group received cariprazine 1.5 mg/day + ADT, the second group received cariprazine 3.0 mg/day + ADT, and the third group received placebo + ADT. For six weeks, the medication was given once daily in addition to the ongoing ADT treatment, to which the patient had experienced inadequate clinical response.

About Study RGH-MD-75
Study RGH-MD-75 is a randomized, double-blind, placebo-controlled, flexible-dose, outpatient, multicenter trial with 808 participants, conducted in United States, Estonia, Finland, Slovakia, Ukraine and Sweden. After 7-14 days of screening and washout of prohibited medications, eligible patients entered an 8-week, double-blind treatment period in which they continued antidepressant treatment and were randomized (1:1:1) to adjunctive cariprazine 1-2 mg/day, cariprazine 2-4.5 mg/day, or placebo. After double-blind treatment, patients entered a 1-week safety follow-up period. Data from Study RGH-MD-75 were published in the *Journal of Clinical Psychiatry*.[5]

More information about studies 3111-301-001, 3111-302-001 and RGH-MD-75 is available at www.clinicaltrials.gov.

About VRAYLAR® (cariprazine)
VRAYLAR® is an oral, once-daily atypical antipsychotic approved for the acute treatment of adults with manic or mixed episodes associated with bipolar I disorder (3 to 6 mg/day) and for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults (1.5 or 3 mg/day). VRAYLAR® is also approved for the treatment of schizophrenia in adults (1.5 to 6 mg/day).

While the mechanism of action of VRAYLAR® is unknown, the efficacy of VRAYLAR® could be mediated through a combination of partial agonist activity at central dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors. Pharmacodynamic studies with cariprazine have shown that it acts as a partial agonist with high binding affinity at dopamine D_3, dopamine D_2, and serotonin 5-HT_{1A} receptors.

Cariprazine demonstrated up to ~8-fold greater *in vitro* affinity for dopamine D_3 vs D_2 receptors. Cariprazine also acts as an antagonist at serotonin 5-HT_{2B} and 5-HT_{2A} receptors with high and moderate binding affinity, respectively as well as it binds to the histamine H_1 receptors.
VRAYLAR® shows lower binding affinity to the serotonin 5-HT_{2C} and α_{1A}- adrenergic receptors and has no appreciable affinity for cholinergic muscarinic receptors. The clinical significance of these *in vitro* data is unknown.

VRAYLAR® is being developed jointly by Gedeon Richter Plc and AbbVie, with AbbVie responsible for commercialization in the U.S., Canada, Japan, Taiwan and certain Latin American countries (including Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Mexico, Peru and Venezuela).

Visit www.vraylar.com for more information.

Important Safety Information about VRAYLAR® (cariprazine)

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR® is not approved for treatment of patients with dementia-related psychosis.

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Safety and effectiveness of VRAYLAR® have not been established in pediatric patients.

Contraindication: VRAYLAR® is contraindicated in patients with known hypersensitivity. Reactions have included rash, pruritus, urticaria, and events suggestive of angioedema.

Cerebrovascular Adverse Reactions, Including Stroke: In clinical trials with antipsychotic drugs, elderly subjects with dementia had a higher incidence of cerebrovascular adverse reactions, including fatalities vs placebo. VRAYLAR® is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with antipsychotic drugs. NMS may cause hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome of potentially irreversible, involuntary, dyskinetic movements) and the likelihood it will become irreversible may increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. If signs and symptoms of TD appear, drug discontinuation should be considered.

Late-Occurring Adverse Reactions: Adverse events may first appear several weeks after initiation of VRAYLAR®, probably because plasma levels of cariprazine and its major metabolites accumulate over time. As a result, the incidence of adverse reactions in short-term trials may not reflect the rates after longer term exposures. Monitor for adverse reactions, including extrapyramidal symptoms (EPS) or akathisia, and patient response for

several weeks after starting VRAYLAR® and after each dosage increase. Consider reducing the dose or discontinuing the drug.

Metabolic Changes: Atypical antipsychotics have caused metabolic changes, such as:

- **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Assess fasting glucose before or soon after initiation of treatment and monitor periodically during long-term treatment.
- **Dyslipidemia:** Atypical antipsychotics cause adverse alterations in lipids. Before or soon after starting an antipsychotic, obtain baseline fasting lipid profile and monitor periodically during treatment.
- **Weight Gain:** Weight gain has been observed with VRAYLAR®. Monitor weight at baseline and frequently thereafter.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia have been reported with antipsychotics, including VRAYLAR®. Agranulocytosis (including fatal cases) has been reported with other antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue VRAYLAR® at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope, with the greatest risk during initial titration and with dose increases. Monitor orthostatic vital signs in patients predisposed to hypotension and in those with cardiovascular/cerebrovascular diseases.

Falls: VRAYLAR® may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures, or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotics and recurrently for patients on long-term therapy.

Seizures: Use VRAYLAR® with caution in patients with history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: Somnolence was reported with VRAYLAR®. Caution patients about performing activities requiring mental alertness (eg, operating hazardous machinery or a motor vehicle).

Body Temperature Dysregulation: Use VRAYLAR® with caution in patients who may experience conditions that increase body temperature (eg, strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics).

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotics. Antipsychotic drugs, including VRAYLAR®, should be used cautiously in patients at risk for aspiration.

Drug Interactions: Strong CYP3A4 inhibitors increase VRAYLAR® concentrations, so VRAYLAR® dose reduction is recommended. Concomitant use with CYP3A4 inducers is not recommended.

Adverse Reactions: In clinical trials, the most common adverse reactions (≥5% and at least twice the rate of placebo) are listed below:

- **Schizophrenia:** The incidences within the recommended dose range (VRAYLAR® 1.5 – 3 mg/day and 4.5 – 6 mg/day vs placebo) were: EPS (15%, 19% vs 8%) and akathisia (9%, 13% vs 4%).
- **Bipolar mania:** The incidences within the recommended dose range (VRAYLAR® 3 – 6 mg/day vs placebo) were: EPS (26% vs 12%), akathisia (20% vs 5%), vomiting (10% vs 4%), dyspepsia (7% vs 4%), somnolence (7% vs 4%), and restlessness (7% vs 2%).
- **Bipolar depression:** The incidences within the recommended doses (VRAYLAR® 1.5 mg/day or 3 mg/day vs placebo) were: nausea (7%, 7% vs 3%), akathisia (6%, 10% vs 2%), restlessness (2%, 7% vs 3%), and EPS (4%, 6% vs 2%).

Please see the full Prescribing Information, including Boxed Warnings, and Medication Guide.

About Richter
Gedeon Richter Plc. (www.richter.hu), headquartered in Budapest/Hungary, is a major pharmaceutical company in Central Eastern Europe, with an expanding direct presence in Western Europe, in China and in Latin America. Having reached a market capitalization of EUR 3.8 billion (USD 4.7billion) by the end of 2020, Richter's consolidated sales were approximately EUR 1.6 billion (USD 1.8 billion) during the same year. The product portfolio of Richter covers many important therapeutic areas, including Women's Healthcare, Central Nervous System and Cardiovascular areas. Having the largest R&D unit in Central Eastern Europe, Richter's original research activity focuses on CNS disorders. With its widely acknowledged steroid chemistry expertise, Richter is a significant player in the Women's Healthcare field worldwide. Richter is also active in biosimilar product development.

References:
1. Abuse, S. (2020). Key substance use and mental health indicators in the United States: results from the 2019 National Survey on Drug Use and Health. Available at: https://www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRPDFWHTML/2019NSDUHFFR1PDFW090120.pdf. Accessed on August 31, 2021.
2. World Health Organization. (2021). Depression. Fact Sheet. Available at: https://www.who.int/news-room/fact-sheets/detail/depression. Accessed on September 16, 2021.
3. Kessler RC, et al. *Psychol Med*. 2010;40:225-237.
4. Greenberg PE, et al. *J Clin Psychiatry*. 2015;76(2):155-162.
5. Durgam S, Earley W, Guo H, Li D, Németh G, Laszlovszky I, Fava M, Montgomery SA. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. J Clin Psychiatry. 2016 Mar;77(3):371-8. doi: 10.4088/JCP.15m10070. PMID: 27046309.

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