Richter and Allergan Announce Positive Topline Results from Third of Three Pivotal Trials of Cariprazine in Bipolar I Depression

Primary endpoint was met in the study evaluating patients with acute bipolar I depression treated with cariprazine 1.5 mg versus placebo

Efficacy and safety of cariprazine in adults with bipolar I depression now supported by positive results from three pivotal clinical trials

BUDAPEST, Hungary and DUBLIN, Ireland – 3 April 2018 – Allergan plc (NYSE:AGN), a leading global pharmaceutical company, and Gedeon Richter Plc., today announced positive topline results for RGH-MD-53, a Phase III study of cariprazine for the treatment of adults with major depressive episodes associated with bipolar I disorder (bipolar I depression). The companies announced in December 2017 positive topline results for the second pivotal trial (RGH-MD-54) of cariprazine in the treatment of bipolar I depression. In that trial both cariprazine 1.5mg and 3mg were statistically greater than placebo.

The efficacy of cariprazine in the treatment of bipolar I depression has been demonstrated in three positive pivotal trials, including RGH-MD-53, RGH-MD-54 and RGH-MD-56. Allergan plans to include data from all three pivotal trials in the Company's Supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) in the second half of 2018.
Cariprazine is currently approved in the U.S. under the brand name VRAYLAR® for the treatment of schizophrenia in adults, and acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

"We are very pleased with the results of our third pivotal study, which reinforce the wealth of data supporting cariprazine as a potential treatment in adults with bipolar depression" said David Nicholson, Chief Research & Development Officer at Allergan. "Bipolar depression is often difficult to treat and can be extremely debilitating for patients. At Allergan, we are committed to developing treatments that address unmet needs facing people living with mental illness and are looking forward to submitting an sNDA for cariprazine for patients suffering with bipolar I depression."

For RGH-MD-53, the primary and key secondary efficacy endpoints were met for the cariprazine 1.5mg dose group. Cariprazine 1.5mg showed a significantly greater improvement than placebo for the change from baseline to week 6 on both the primary efficacy parameter the Montgomery-Asberg Depression Rating Scale (MADRS) total score (p=0.0417, LSMD -2.5), as well as the key secondary parameter, Clinical Global Impression Scale-Severity (CGI-S) (p=0.0417, LSMD -0.3). Cariprazine 3mg showed a numerical improvement over placebo for both the primary (p=0.1051, LSMD -1.8) and secondary parameters (p=0.1370, LSMD -0.2), but did not reach statistical significance.

“Treating bipolar depression can be very difficult given the few therapies available to manage these symptoms of bipolar I disorder. Further, there are a limited number of products available to help treat the full range of bipolar disorder – from mania through depression,” said Gary Sachs, MD, Associate Clinical Professor of Psychiatry at Harvard Medical School. “This data is encouraging for patients and the broader psychiatry community, as it demonstrates cariprazine’s potential in treating the full spectrum of the disorder.”

In this study, 493 patients were randomized (1:1:1) to placebo, cariprazine 1.5mg and cariprazine 3mg treatment groups to evaluate the efficacy, safety and tolerability of cariprazine in patients with bipolar I depression. Cariprazine was generally well tolerated in the trial. The overall incidence of patients who experienced adverse events was 51 percent for the cariprazine 1.5 and 3mg dose groups, and 46 percent for the placebo group. The majority of adverse events were mild to moderate and led to discontinuation in approximately 5 percent of cariprazine treated patients versus 3 percent of placebo treated patients. The most commonly reported adverse events in the cariprazine groups were akathisia, restlessness, nausea, and fatigue.

"Today’s positive results provide further support for the therapeutic value of cariprazine, one of our flagship products. We are encouraged by the findings, which mark a major step forward in making this promising treatment option available for patients suffering from bipolar depression," added Dr. István Greiner, Research Director of Gedeon Richter Plc.

About Cariprazine in Bipolar I Depression

RGH-MD-56 was a Phase II, randomized, double-blind, placebo-controlled, parallel-group clinical trial in adult patients with bipolar I depression. A total of 584 patients were randomized to evaluate the efficacy, safety, and tolerability of cariprazine 0.75 mg, 1.5mg and 3mg compared to placebo in the treatment of outpatients with bipolar I depression. Patients underwent a no-drug screening period of approximately 7-14 days, followed by 8 weeks of double-blind treatment (primary endpoint was 6-weeks) and a 1-week, no investigational product safety follow-up period.

RGH-MD-53 and RGH-MD-54 were identical Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter, fixed-dose clinical trials in adult patients with bipolar I depression. Patients were randomized in both studies aiming to evaluate the efficacy, safety, and tolerability of cariprazine 1.5mg and 3mg compared to placebo in outpatients with bipolar I depression. Patients underwent a no-drug screening period of approximately 7-14 days, followed by 6 weeks of double-blind treatment and a 1-week, no investigational product safety follow-up period.

About VRAYLAR® (cariprazine)

VRAYLAR is an oral, once daily atypical antipsychotic approved for the acute treatment of adult patients with manic or mixed episodes associated with bipolar I disorder, with a recommended dose range of 3 to 6 mg/day, and for the treatment of schizophrenia in adults, with a recommended dose range of 1.5 to 6 mg/day.

While the mechanism of action of VRAYLAR in schizophrenia and bipolar I disorder 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. Cariprazine 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 was discovered and co-developed by Gedeon Richter Plc. and is licensed by Allergan, in the U.S. and Canada. For more than a decade both companies have conducted over 20 clinical trials enrolling thousands of patients worldwide to evaluate the efficacy and safety of cariprazine for patients suffering from a broad range of mental health illnesses.

Visit www.vraylar.com for more information.

About Allergan plc

Allergan plc (NYSE: AGN), headquartered in Dublin, Ireland, is a bold, global pharmaceutical company and a leader in a new industry model – Growth Pharma. Allergan is focused on developing, manufacturing and commercializing branded pharmaceutical, device, biologic, surgical and regenerative medicine products for patients around the world.

Allergan markets a portfolio of leading brands and best-in-class products for the central nervous system, eye care, medical aesthetics and dermatology, gastroenterology, women's health, urology and anti-infective therapeutic categories.

Allergan is an industry leader in Open Science, a model of research and development, which defines our approach to identifying and developing game-changing ideas and innovation for better patient care. With this approach, Allergan has built one of the broadest development pipelines in the pharmaceutical industry.

Allergan's success is powered by our global colleagues' commitment to being Bold for Life. Together, we build bridges, power ideas, act fast and drive results for our customers and patients around the world by always doing what is right.

With commercial operations in approximately 100 countries, Allergan is committed to working with physicians, healthcare providers and patients to deliver innovative and meaningful treatments that help people around the world live longer, healthier lives every day.

For more information, visit Allergan's website at www.Allergan.com.

Forward-Looking Statement

Statements contained in this press release that refer to future events or other non-historical facts are forward-looking statements that reflect Allergan's current perspective on existing trends and information as of the date of this release. Actual results may differ materially from Allergan's current expectations depending upon a number of factors affecting Allergan's business. These factors include, among others, the difficulty of predicting the timing or outcome of FDA approvals or actions, if any; the impact of competitive products and pricing; market acceptance of and continued demand for Allergan's products; the impact of uncertainty around timing of generic entry related to key products, including RESTASIS®, on our financial results; uncertainty associated with financial projections, projected cost reductions, projected synergies, restructurings, increased costs, and adverse tax consequences; difficulties or delays in manufacturing; and other risks and uncertainties detailed in Allergan's periodic public filings with the Securities and Exchange Commission, including but not limited to Allergan's Annual Report on Form 10-K for the year ended 31 December 2017. Except as expressly required by law, Allergan disclaims any intent or obligation to update these forward-looking statements.

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 capitalisation of EUR 4.1 billion (US$ 4.9 billion) by the end of 2017, Richter's consolidated sales were approximately EUR 1.4 billion (US$ 1.6 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.

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