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Shire Reports Findings From an Analysis Examining Emotional Lability in Children With ADHD Taking VYVANSE[®] (lisdexamfetamine dimesylate) Capsules CII

Post hoc analysis of Phase 3 study data presented at national psychiatric meeting

PHILADELPHIA – November 12, 2009 – [Shire plc](#) (LSE: SHP, NASDAQ: SHPGY), the global specialty biopharmaceutical company, announced findings from a post hoc analysis examining emotional lability from Phase 3 study data with [VYVANSE[®]](#). In this study, VYVANSE demonstrated significant improvement in Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms as measured by the ADHD Rating Scale IV (ADHD-RS IV) and Connors' Parent Rating Scale-Revised Short (CPRS-RS) in children with ADHD aged 6 to 12 years. The post hoc analysis showed that patients demonstrated an improvement in emotional lability composite CPRS-RS scores while taking VYVANSE as compared to placebo. These results were presented recently at a psychiatric meeting in Honolulu.

"Children taking ADHD medications can experience emotional lability, often described as frequent changes in emotions or mood. Therefore, evaluating the impact of ADHD treatments, including VYVANSE, on children's emotional lability may be important for parents and health care professionals when assessing a child's treatment plan," said Ann C. Childress, MD, study investigator and president of the Center for Psychiatry and Behavioral Medicine, Inc. in Las Vegas.

About the Analysis and Study

This post hoc analysis was based on a Phase 3, randomized, double-blind, placebo-controlled trial with forced-dose escalation of VYVANSE (30, 50, or 70 mg/d) or placebo in 285 children aged 6 to 12 years with ADHD. The primary end point of the study was the ADHD-RS IV, and secondary end points included CPRS-RS and safety. The CPRS-RS scale in its entirety contains 27 items to evaluate children's behaviors based on parents' responses. Each of the CPRS-RS 27 items is scored from zero as "Not At All True/Never, Seldom" up to three as "Very Much True/Very Often, Very Frequent." Parents completed the CPRS at 10 AM, 2 PM, and 6 PM at study start and on the day before their children made the weekly study visits. In the post hoc analysis, the children's emotional lability score was determined based on the sum of their average scores from three items on the CPRS-RS: angry/resentful, loses temper, and irritable. Patients were then grouped into those with and without prominent emotional lability at study start (scores greater than three versus scores of three or less) so that each group could be evaluated separately.

Overall, the children's average emotional lability scores significantly improved with VYVANSE treatment compared with placebo across the day (10 AM, 2 PM, and 6 PM) from study start to end (all $P \leq .0004$).

As expected, treatment with VYVANSE, compared to placebo, did not result in significant improvements in emotional lability scores from study start to end in those without prominent emotional lability prior to treatment. However, treatment with VYVANSE, compared to placebo, yielded significant improvements in the emotional lability scores of those children with prominent emotional lability ($P < .0001$).

The most common treatment-emergent adverse events reported in this study for patients taking VYVANSE were decreased appetite, insomnia, upper abdominal pain, headache, irritability, vomiting, weight decrease, nausea, dizziness, and dry mouth.

VYVANSE, which was introduced in the United States in July 2007 for the treatment of ADHD in children aged 6 to 12 years and approved in April 2008 to treat ADHD in adults, is currently available in six dosage strengths of 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

VYVANSE is a therapeutically inactive prodrug stimulant, in which *d*-amphetamine is covalently bonded to l-lysine, and after oral ingestion it is converted to pharmacologically active *d*-amphetamine. The conversion of VYVANSE to *d*-amphetamine is not affected by gastrointestinal pH and is unlikely to be affected by alterations in GI transit times.

Additional information about VYVANSE and Full Prescribing Information, including the Medication Guide, are available at <http://www.vyvance.com>.

About VYVANSE

VYVANSE is indicated for the treatment of ADHD. Efficacy based on two controlled trials in children aged 6 to 12 and one controlled trial in adults.

VYVANSE should not be taken by patients who have advanced arteriosclerosis; symptomatic cardiovascular disease; moderate to severe hypertension; hyperthyroidism; known hypersensitivity or idiosyncrasy to sympathomimetic amines; agitated states; glaucoma; a history of drug abuse; or during or within 14 days after treatment with monoamine oxidase inhibitors (MAOIs).

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses in ADHD. Physicians should take a careful patient history, including family history, and physical exam, to assess the presence of cardiac disease. Patients who report symptoms of cardiac disease such as exertional chest pain and unexplained syncope should be promptly evaluated. Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate.

New psychosis, mania, aggression, growth suppression, and visual disturbances have been associated with the use of stimulants. Use with caution in patients with a history of psychosis, seizures or EEG abnormalities, bipolar disorder, or depression. Growth should be monitored in children during treatment with stimulants, and patients who are not growing (gaining height or weight) as expected may need to have their treatment interrupted.

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic uses or distribution to others and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events.

The most common adverse events reported in clinical studies of VYVANSE were: *pediatric* – decreased appetite, insomnia, abdominal pain, and irritability; *adult* – decreased appetite, insomnia, and dry mouth.

About ADHD

ADHD is one of the most common psychiatric disorders in children and adolescents. Worldwide prevalence of ADHD is estimated at 5.3 percent (with large variability), according

to a comprehensive systematic review of this topic published in 2007 in the *American Journal of Psychiatry*. In the United States, approximately 7.8 percent of all school-aged children, or about 4.4 million children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the Centers for Disease Control and Prevention (CDC). The disorder is also estimated to affect 4.4 percent of US adults aged 18 to 44 based on results from the National Comorbidity Survey Replication. When this percentage is extrapolated to the full US population aged 18 and over, almost 10 million adults are believed to have ADHD.

ADHD is a psychiatric behavioral disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. The specific etiology of ADHD is unknown and there is no single diagnostic test for this disorder. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources, utilizing diagnostic criteria such as *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV®)* or *International Classification of Diseases 10 (ICD-10)*.

Although there is no cure for ADHD, there are accepted treatments that specifically target its symptoms. Standard treatments include educational approaches, psychological or behavioral modification, and/or medication.

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SHIRE PLC

Shire's strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit hyperactivity disorder (ADHD), human genetic therapies (HGT) and gastrointestinal (GI) diseases as well as opportunities in other therapeutic areas to the extent they arise through acquisitions. Shire's in-licensing, merger and acquisition efforts are focused on products in specialist markets with strong intellectual property protection and global rights. Shire believes that a carefully selected and balanced portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

For further information on Shire, please visit the Company's Web site: <http://www.shire.com>.

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Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, the Company's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of research, development, approval, reimbursement, manufacturing and commercialization of the Company's Specialty Pharmaceutical and Human Genetic Therapies products, as well as the ability to secure and integrate new products for commercialization and/or development; government regulation of the Company's products; the Company's ability to manufacture its products in sufficient quantities to meet demand; the impact of competitive therapies on the Company's products; the Company's ability to register, maintain and enforce patents and other intellectual property rights relating to its products; the Company's ability to obtain and maintain government and other third-party reimbursement for its products; and other risks and uncertainties detailed from time to time in the Company's filings with the Securities and Exchange Commission.