Press Release

www.shire.com

Positive Top-line Results Shown for Vyvanse® (lisdexamfetamine dimesylate) Capsules (CII) in Adults with Binge Eating Disorder

Shire Plans to Submit a Supplemental New Drug Application (sNDA) by Q3 2014

05 November 2013 – Shire plc (LSE: SHP, NASDAQ: SHPG) announces positive top-line results from two identically designed randomized placebo-controlled Phase 3 studies evaluating the efficacy and safety of Vyvanse® (lisdexamfetamine dimesylate) Capsules (CII) versus placebo in adults with binge eating disorder (BED). In both studies Vyvanse was found to be statistically superior to placebo on the primary efficacy analysis (p-value <0.001) of the change from baseline at weeks 11 to 12 in terms of number of binge days per week. The safety for Vyvanse in these two studies appears to be generally consistent with the known profile established in studies in adults with Attention-Deficit/Hyperactivity Disorder (ADHD). The Company is reporting the data sooner than originally anticipated because of faster than expected completion of both studies.

"We are extremely pleased with these results, and will be working expeditiously to submit an application to the U.S. Food and Drug Administration for a new indication of BED for Vyvanse, already well established for its efficacy and safety in ADHD," said Flemming Ornskov, M.D., Chief Executive Officer, Shire. "BED is a condition for which there is no currently approved pharmacologic treatment and yet there is significant unmet patient need, as was demonstrated with the faster than expected enrollment of participants in our clinical trial program. Our development of Vyvanse for BED also aligns well with Shire's growth strategy of developing innovative treatments to address significant unmet patient needs."

In addition to the positive top-line primary results, both studies showed statistically significant (p-value <0.001) and consistent treatment effects for Vyvanse across the key secondary efficacy endpoints that have been analyzed thus far in the top-line data. These include the Clinical Global Impressions – Global Improvement (CGI-I), 4-week binge cessation, percent change from baseline in body weight, and change from baseline in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE). Additional analyses continue for other secondary endpoints. Shire anticipates presenting the efficacy and safety data from both studies at a major scientific meeting in 2014. The company plans to file for FDA regulatory approval of Vyvanse for the treatment of BED in adults (ages 18 to 55) by Q3 2014.

Vyvanse is a prescription medicine currently only approved for the treatment of ADHD in the United States, Canada, Australia, several European countries (trade name: Elvanse®/Tyvense®) and Brazil (trade name: Venvanse™). Vyvanse should only be used in accordance with locally approved prescribing information.

CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

BED has a lifetime prevalence of 2.8 percent in adults in the United States, and is characterized by recurring episodes of binge eating, feeling out of control while binging, and feeling guilt and shame afterward. It is formally recognized as a distinct psychiatric disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*™).

“Binge eating disorder is an important public health problem that is under-recognized, and causes great distress for patients,” said Susan L. McElroy, M.D., Professor of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine; and principal investigator of both studies. “Increased awareness of binge eating disorder among the medical community is greatly needed, as are novel treatment strategies for individuals suffering from this often secretive disorder.”

ABOUT THE BED STUDIES

Each of the two identically designed pivotal Phase 3, multi-center, randomized, double-blind, parallel-group, placebo-controlled, dose-optimized studies was designed to assess the safety, efficacy, and tolerability of Vyvanse in patients aged 18 to 55 who met *DSM-IV-TR*® criteria for a diagnosis of BED. Study SPD489-343 randomized 383 patients and study SPD489-344 randomized 390 patients. Patients were randomized in a 1:1 ratio to Vyvanse or placebo. The primary efficacy endpoint for these studies was defined as the change from baseline to Weeks 11 - 12 (Visit 8) in the number of binge days per week determined by clinical interview based on participant diary data. Vyvanse was statistically superior to placebo on the primary efficacy analysis for both studies.

Safety and tolerability evaluations of Vyvanse included treatment-emergent adverse events (TEAEs), vital signs, weight, and electrocardiograms (ECGs).

The key secondary endpoints analyzed to date included CGI-I, 4-week binge cessation, percent change from baseline in body weight, and change from baseline in Y-BOCS-BE. The CGI-I was dichotomized as improved (including categories of ‘very much improved’ and ‘much improved’) or not improved (other categories excluding ‘not assessed’). The endpoint 4-week cessation of binge eating is defined as no binge episodes for 28 consecutive days prior to the last study visit. The Y-BOCS-BE is a modified version of Yale-Brown Obsessive Compulsive Scale that measures the obsession of binge eating thoughts and compulsiveness of binge eating behaviors. Vyvanse was statistically superior to placebo on the key secondary efficacy endpoints analyzed to date for both studies.

<u>Study SPD489-343</u>
In study SPD489-343 there were 3 patients treated with Vyvanse who reported serious adverse events (SAEs); 2 patients treated with placebo reported SAEs. There were 12 patients on Vyvanse who reported treatment-emergent adverse events (TEAEs) that led to study discontinuation; 5 patients on placebo reported TEAEs that led to study discontinuation. The most commonly reported (>=5% of patients) TEAEs in patients taking Vyvanse included dry mouth, insomnia, headache, decreased appetite, nausea, irritability, heart rate increased, anxiety, feeling jittery, constipation, hyperhidrosis.

<u>Study SPD489-344</u>
In study SPD489-344 there was 1 patient treated with Vyvanse who reported a serious adverse event (SAE); 2 patients treated with placebo-reported SAEs. There were 7 patients on Vyvanse reported TEAEs that led to study discontinuation; 4 patients on placebo reported TEAEs that led to study discontinuation. The most commonly reported (>=5% of patients) TEAEs in patients taking Vyvanse included dry mouth, headache, insomnia, fatigue, nausea, diarrhoea, decreased appetite, constipation, feeling jittery, blood pressure increased, and irritability.

There were no deaths in either of the studies.

Further evaluation of the safety information related to vital signs, ECG, clinical laboratory and other safety assessments results is currently underway.

The safety profile for Vyvanse in these two studies, based on top-line data, appears to be generally consistent with the known profile established in studies in adults with ADHD.

The studies consisted of a minimum 2-week screening period, a 12-week treatment phase (4 weeks of dose-optimization and 8 weeks of maintenance), and a follow-up visit 1 week after the last on-treatment visit. During the screening period, eligible patients demonstrated BED of at least moderate severity, defined in the study protocol as at least three or more binge days per week, for each of the 2 weeks prior to baseline, per diary entries. Patients were randomized to Vyvanse or placebo treatment groups. During the dose optimization period, all Vyvanse-treated patients were initiated at the 30-mg dose, and then titrated in 20-mg increments to their optimal dose (either 50 or 70mg).

Patients were excluded if they had a concurrent diagnosis of bulimia nervosa, anorexia nervosa, other psychiatric disorders, or certain medical co-morbidities (e.g., cardiovascular risk, moderate to severe hypertension, diabetes mellitus); a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of 18 or more at baseline visit; a lifetime history of amphetamine, cocaine, or other stimulant abuse and/or dependence.

RESEARCH CRITERIA FOR BED DIAGNOSIS

Both clinical trials used the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR®)* research criteria for BED. *DSM-IV-TR®* research criteria for BED, as set forth in Appendix B (Criteria Sets and Axes Provided for Further Study), characterizes the disorder by recurrent episodes of eating unusually large amounts of food in a short period of time (e.g., within a 2-hour period), a sense of lack of control over the act of eating during the episode, and marked distress. BED episodes also are associated with at least three of the following: eating more rapidly than normal; eating until feeling uncomfortably full; eating large amounts of food when not feeling physically hungry; often eating alone because of embarrassment by how much food is being eaten; feeling disgusted with oneself, depressed or guilty after overeating. Binge eating occurs, on average, at least two days a week for six months. The episodes of binge eating do not occur exclusively during the course of bulimia nervosa or anorexia nervosa.
The recently published *DSM-5*™ (May 2013) includes BED as a formal Eating Disorder diagnosis. *DSM-5*™requires that binge eating occurs on average at least once a week for three months.

SHIRE PIPELINE UPDATE

In light of the early availability of top-line data for the BED phase 3 program, Shire has reviewed timelines for two other major phase 3 programs: lifitegrast in Dry Eye Disease and Vyvanse as an adjunctive treatment in Major Depressive Disorder (MDD). The Company now anticipates that top-line data from OPUS 2 for lifitegrast could become available before the end of 2013. The Sonata safety study for lifitegrast is scheduled for completion by mid-2014. The MDD program for Vyvanse is also on track for completion in the first half of 2014.

ABOUT Vyvanse® (lisdexamfetamine dimesylate)

INDICATION

Vyvanse is indicated for the treatment of ADHD in patients ages 6 and above. Efficacy was established in short-term controlled studies in children aged 6 to 17 and in adults. Vyvanse is also approved as a maintenance treatment for patients ages 6 and above with ADHD based on one maintenance study in patients aged 6 to 17 and one maintenance study in adults.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence.

Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

- Contraindications:
  - Known hypersensitivity to amphetamines or other ingredients in Vyvanse. Anaphylactic reactions, Stevens - Johnson syndrome, angioedema, and urticaria have been observed in postmarketing reports.
  - Concurrent administration of monoamine oxidase inhibitors (MAOI) or administration of Vyvanse within 14 days of the last MAOI dose. Hypertensive crisis can occur.
- Educate patients about abuse and periodically re-evaluate the need for Vyvanse.
- Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Prior to treatment assess for the presence of cardiac disease. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Vyvanse treatment.
- CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.
- Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with preexisting psychosis. Clinical evaluation for bipolar disorder is recommended prior to stimulant use.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Monitor weight and height in children during treatment with Vyvanse. Treatment may need to be interrupted in children not growing as expected.
- Stimulants used to treat ADHD, including Vyvanse, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes (e.g., numbness, pain, skin color change, or sensitivity to temperature, and rarely ulcerations and/or soft tissue breakdown) is necessary during treatment and may require further evaluation (e.g., referral).
- The most common adverse reactions (≥5% and at least twice the rate of placebo) reported in clinical trials were:
  - *Children aged 6 to 12*: decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, decreased weight, nausea, dry mouth and dizziness;

- *Adolescents aged 13 to 17*: decreased appetite, insomnia, and decreased weight;
- *Adults*: decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety and anorexia.

Please click here for Full Prescribing Information.

For further information please contact:

Investor Relations		
Eric Rojas	erojas@shire.com	+1 781 482 0999
Sarah Elton-Farr	seltonfarr@shire.com	+44 1256 894157
Media		
Jessica Mann	jmann@shire.com	+44 1256 894 280
Gwen Fisher	gfisher@shire.com	+1 484 595 9836

NOTES TO EDITORS

Shire enables people with life-altering conditions to lead better lives.

Our strategy is to focus on developing and marketing innovative specialty medicines to meet significant unmet patient needs.

We provide treatments in Neuroscience, Rare Diseases, Gastrointestinal, Internal Medicine and Regenerative Medicine, and we are developing treatments for symptomatic conditions treated by specialist physicians in other targeted therapeutic areas.

www.shire.com

FORWARD - LOOKING STATEMENTS - "SAFEHARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included in this announcement that are not historical facts are forward-looking statements. 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, Shire's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, that:

- Shire's products may not be a commercial success;
- revenues from ADDERALL XR are subject to generic erosion;
- the failure to obtain and maintain reimbursement, or an adequate level of reimbursement, by third-party payors in a timely manner for Shire's products may impact future revenues and earnings;
- Shire relies on a single source for manufacture of certain of its products and a disruption to the supply chain for those products may result in Shire being unable to

continue marketing or developing a product or may result in Shire being unable to do so on a commercially viable basis;

- Shire uses third party manufacturers to manufacture many of its products and is reliant upon third party contractors for certain goods and services, and any inability of these third party manufacturers to manufacture products, or any failure of these third party contractors to provide these goods and services, in each case in accordance with its respective contractual obligations, could adversely affect Shire's ability to manage its manufacturing processes or to operate its business;
- the development, approval and manufacturing of Shire's products is subject to extensive oversight by various regulatory agencies and regulatory approvals or interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;
- the actions of certain customers could affect Shire 's ability to sell or market products profitably and fluctuations in buying or distribution patterns by such customers could adversely impact Shire's revenues, financial conditions or results of operations;
- investigations or enforcement action by regulatory authorities or law enforcement agencies relating to Shire's activities in the highly regulated markets in which it operates may result in the distraction of senior management, significant legal costs and the payment of substantial compensation or fines;
- adverse outcomes in legal matters and other disputes, including Shire's ability to obtain, maintain, enforce and defend patents and other intellectual property rights required for its business, could have a material adverse effect on Shire's revenues, financial condition or results of operations;

and other risks and uncertainties detailed from time to time in Shire's filings with the U.S. Securities and Exchange Commission, including its most recent Annual Report on Form 10K.