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Shire Reports Tolerability and Clinical Effects Results of DAYTRANA[®] (methylphenidate transdermal system) from Study in Adolescents with ADHD

Additional DAYTRANA data on pharmacokinetics also presented at national psychiatric meeting

HONOLULU – October 30, 2009 – [Shire plc](#) (LSE: SHP, NASDAQ: SHPGY), the global specialty biopharmaceutical company, today announced findings at a major medical meeting from a Phase IIIb study of the tolerability and effectiveness of [DAYTRANA[®]](#) (methylphenidate transdermal system) in adolescents aged 13 to 17 years diagnosed with Attention-Deficit/Hyperactivity Disorder ([ADHD](#)). In addition, data regarding the pharmacokinetic profile of DAYTRANA in children and adolescents was also presented. DAYTRANA, the first and only patch for the treatment of ADHD, is indicated for use in children aged 6 to 12 years with the disorder.

Alain Katic, MD, child psychiatrist at the Claghorn Research Clinic in Houston, Texas, states, “In this 6-month, open-label adolescent extension study, we found that most adverse events were generally mild to moderate in intensity. Additionally, DAYTRANA treatment resulted in significant improvements in ADHD Rating Scale IV mean total scores from baseline to end point.”

[DAYTRANA](#) delivers medication directly through the skin into the bloodstream and is designed to release methylphenidate continuously while applied to the skin. DAYTRANA is approved by the US Food and Drug Administration (FDA) for a wear-time of nine hours; however, the patch can be removed earlier to accommodate changing schedules or to help manage late day side effects, allowing parents, working with physicians, to tailor the treatment to a child's specific needs. DAYTRANA is available in 10-mg, 15-mg, 20-mg, and 30-mg patches.

“As a leader in ADHD treatment, Shire is proud to offer treatment options to help meet the various needs of patients diagnosed with ADHD. Once-daily [DAYTRANA](#) is a transdermal alternative to oral immediate- and extended-release formulations of methylphenidate, an active ingredient that has been used to treat ADHD for over 50 years,” said Michael Yasick, Senior Vice President of the ADHD Business Unit at Shire. “The short term efficacy and safety profile of DAYTRANA in adolescents has been previously reported and this Shire-supported study examined the tolerability and effectiveness of the medication in the adolescent population over an extended period of six months.”

Long-Term Open-Label Tolerability and Effectiveness Study in Adolescents with ADHD

In this study, DAYTRANA participants were titrated to their optimal dose over five weeks and were then maintained on that dose for an additional five months. Participants from a previous double-blind, seven week study were able to enroll. In this seven week study, DAYTRANA was shown to significantly improve ADHD symptoms as rated by clinicians and parents compared with placebo. The frequency of adverse events was typical of those seen in studies of oral methylphenidate in adolescents, with the exception of dermal reactions. The long term extension study evaluated four doses of the DAYTRANA patch worn for nine

hours at alternating hips and used for about six months. Most adverse events were mild to moderate in intensity. The most commonly reported treatment-emergent adverse events reported by 5 percent or more of participants that received DAYTRANA were decreased appetite (11.0 percent); headache (10.1 percent); upper respiratory tract infection (10.1 percent); nasopharyngitis (inflammation of the nasal passages and of the upper part of the pharynx) (9.2 percent); and irritability (5.5 percent). The majority (93.6 percent) of skin response scores were defined as no irritation or minimal to definite redness.

The primary effectiveness measure was the change from baseline to end point of the total mean ADHD Rating Scale IV (ADHD-RS-IV) score. The baseline was defined as the baseline from the previous double-blind study and the end point was defined as the last assessment for which a valid ADHD-RS-IV score was obtained. The ADHD-RS-IV scale contains 18 items and is based on the ADHD diagnostic criteria as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*[®], a publication of the American Psychiatric Association.

DAYTRANA demonstrated significant improvement in the overall mean (\pm SD) change in ADHD-RS-IV total score from antecedent study baseline to end point of this study of -23.0 (\pm 10.77) $P < .001$. In addition, the average ADHD-RS-IV mean total scores decreased from this study start to end from 19.8 to 13.8 ($P < .001$).

Pharmacokinetic Study in Children and Adolescents with ADHD

The pharmacokinetic profile of DAYTRANA has been previously reported for children aged 6 to 12 years; the data presented today are the first to report DAYTRANA pharmacokinetics that also included an adolescent population aged 13 to 17 years.

In this one-month, open-label, multiple-phase study, investigators randomized 35 children and 36 adolescents who received either DAYTRANA (single, multiple fixed, and multiple escalating doses, each worn for nine hours), or OROS MPH. The study's four phases were single dosing, multiple fixed dosing, dose escalation, and follow-up.

Following single and multiple fixed or escalating doses, systemic exposure was greater in children compared with adolescents, and was consistent with their lower body weights. As a result of accumulation, systemic exposure to α -MPH in children after multiple escalating doses was 1.4- to 1.6-fold higher for DAYTRANA compared with OROS MPH, but in adolescents was similar for the two formulations.

All treatment-emergent adverse events were of mild to moderate intensity and none led to discontinuation from the study. No deaths or serious adverse events were reported.⁵ Eighteen children reported at least one treatment-emergent adverse event, and the most frequently reported was decreased appetite (27.3 percent of participants receiving OROS MPH and 8.3 percent of participants receiving both escalating doses and multiple fixed doses of DAYTRANA). Nineteen adolescents reported at least one treatment-emergent adverse event, and the most frequently reported was headache (27.3 percent of participants receiving OROS MPH and 16.7 percent of participants receiving escalating doses of DAYTRANA, and none of the participants receiving multiple fixed doses of DAYTRANA).

This study was not designed to make comparisons between DAYTRANA and OROS MPH.

Important Safety Information about DAYTRANA

DAYTRANA is indicated for the treatment of ADHD in children aged 6 to 12 years.

DAYTRANA should not be used in patients with allergy to methylphenidate or patch components; marked anxiety, tension and agitation; glaucoma; tics, diagnosis or a family history of Tourette's syndrome; seizures; 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 deaths, 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; EEG abnormalities; bipolar disorder; depression. Hematologic monitoring is advised during prolonged treatment. Patients should avoid applying external heat to the DAYTRANA patch. Erythema has been commonly reported. Contact sensitization may occur. 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.

DAYTRANA should be given cautiously to patients with a history of drug dependence and alcoholism. Chronic abuse can lead to marked tolerance and psychological dependence. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder.

Common adverse events reported by patients who received DAYTRANA in clinical trials were decreased appetite, insomnia, nausea, vomiting, decreased weight, tics, affect lability, and anorexia, consistent with adverse events commonly associated with the use of methylphenidate.

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).

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 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>.

THE "SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

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.

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