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Shire Announces Publication of Open-Label Study on Coadministration of INTUNIV™ (guanfacine) Extended-Release Tablets with Stimulants

Primary objective of the study was to evaluate the safety of coadministration of INTUNIV with stimulants

PHILADELPHIA – November 16, 2009 – [Shire plc](#) (LSE: SHP, NASDAQ: SHPGY), the global specialty biopharmaceutical company, announced new study results on [INTUNIV™](#) (guanfacine) Extended-Release Tablets published in the October *Journal of Child and Adolescent Psychopharmacology*. In this open-label safety study, there was no evidence of unique adverse effects with the combination of INTUNIV and amphetamine or methylphenidate relative to what was observed with either medication alone. The open-label study also assessed improvement of Attention-Deficit/Hyperactivity Disorder ([ADHD](#)) symptoms using the ADHD Rating Scale-IV (ADHD-RS-IV). INTUNIV is a nonscheduled, once-daily selective alpha-2A agonist indicated for monotherapy treatment of ADHD in children and adolescents ages 6 to 17.

“Pivotal studies have shown that INTUNIV improved ADHD symptoms in children and adolescents with the disorder, and the publication of these safety data gives us insight into administering INTUNIV in combination with stimulant medications in the management of ADHD,” said Andrew J Cutler, MD, courtesy assistant professor, department of psychiatry, University of Florida, and CEO and medical director, Florida Clinical Research Center, Bradenton, FL. “This study helped inform the design of a controlled coadministration trial of INTUNIV with stimulant medications, which Shire is currently conducting.”

An estimated 25 to 30 percent of ADHD patients may not respond to the most commonly prescribed ADHD medications, methylphenidates and amphetamines, when used alone as ADHD treatment.

About the Coadministration Study

This nine-week, open-label, multicenter, dose-escalation study assessed the safety and effectiveness of coadministering INTUNIV with stimulant medications (methylphenidate or amphetamine). The enrolled patient population included 75 children and adolescents ages 6 to 17 diagnosed with ADHD whose ADHD symptoms were suboptimally controlled after at least one month of treatment with these stimulants. Investigators then started subjects at 1 mg/day of INTUNIV and increased the dose each week by 1 mg to the highest tolerated dose (1 mg/day, 2 mg/day, 3 mg/day, or 4 mg/day). Throughout the INTUNIV titration and maintenance phases of the study, subjects remained on the current dose of their stimulant medication.

The study met its primary objective which was to evaluate the safety of coadministration of INTUNIV (up to 4 mg/day) with stimulants. The study safety assessments included adverse events (AEs), vital signs, electrocardiogram (ECG) readings, physical examination, clinical laboratory tests, the Pediatric Daytime Sleepiness Scale (PDSS), and the Pittsburgh Side Effects Rating Scale (PSERS). AEs were generally mild to moderate. The most common treatment-emergent AEs seen with coadministration (>10.0 percent) were fatigue (34.7 percent), headache (33.3 percent), upper abdominal pain (32.0 percent), irritability (32.0 percent). [Registered in Jersey, No. 99854, 22 Grenville Street, St Helier, Jersey JE4 8PX](#)

percent), somnolence (18.7 percent), and insomnia (16.0 percent). The most common treatment-emergent AEs that investigators deemed were possibly related or related to INTUNIV when given with either stimulant were upper abdominal pain (25.3 percent), fatigue (24.0 percent), irritability (22.7 percent), headache (20.0 percent), somnolence (18.7 percent), and insomnia (13.3 percent). Similar proportions of both treatment groups (INTUNIV and amphetamine or INTUNIV and methylphenidate) experienced these treatment-emergent AEs. Blood pressure decreases, though frequent, were rarely rated by investigators as AEs: two subjects (2.7 percent) had decreased blood pressure and one (1.3 percent) had unspecified hypotension. There were no serious AEs or deaths.

Furthermore, coadministration of INTUNIV with methylphenidate or amphetamine did not increase sleepiness, as noted by the decrease in PDSS scores assessed at visit six and at the end of the study.

Study results also demonstrated statistically significant mean changes from baseline (stimulant monotherapy just prior to receiving INTUNIV) to end point in ADHD-RS-IV total scores. Secondary efficacy end points included subjects' scores on the Conners' Parent Rating Scale-Revised Short Form (CPRS-R), Clinical Global Impression-Severity and Improvement scales (CGI-S and CGI-I), Parent Global Assessment (PGA) scale, and Child-Health Questionnaire-Parent Form (CHQ-PF50).

INTUNIV is not approved for coadministration with other ADHD medications.

Shire Development Inc. supported this study.

Additional information about INTUNIV and Full Prescribing Information are available at www.intuniv.com

Important Safety Information

INTUNIV is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents aged 6 to 17. Efficacy was established in two controlled clinical trials (8 and 9 weeks in duration). The physician electing to use INTUNIV for extended periods should periodically reevaluate its long-term usefulness for the individual patient.

INTUNIV should not be used in patients with a history of hypersensitivity to guanfacine or any of its inactive ingredients or by patients taking other products containing guanfacine.

Hypotension, bradycardia, and syncope were observed in clinical trials. Use INTUNIV with caution in treating patients who have experienced hypotension, bradycardia, heart block, or syncope, or who may have a condition that predisposes them to syncope; are treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope. Heart rate and blood pressure should be measured prior to initiation of therapy, following dose increases, and periodically while on therapy. Patients should be advised to avoid becoming dehydrated or overheated.

Sedation and somnolence were commonly observed in clinical trials. The potential for additive sedative effects with CNS depressant drugs should be considered. Patients should be cautioned against operating heavy equipment or driving until they know how they respond to INTUNIV. Avoid use with alcohol.

Common adverse reactions in patients taking INTUNIV that may be dose related over the range of 1 to 4 mg/day include somnolence, sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth, and constipation.

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/or medication.

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Notes to editors

ADHD-RS-IV is a standardized, validated test for assessing symptoms of ADHD and for assessing response to treatment. The scale, which contains 18 items, 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.

CGI is a standard assessment used to rate the severity of a patient's illness and improvement over time. For the CGI-S, the clinician rated the severity of ADHD symptoms at baseline on a scale of 1 (no symptoms) to 7 (very severe symptoms). For the CGI-I, the clinician rated the improvement of ADHD symptoms at visit 6 on a scale of 1 (very much improved) to 7 (very much worse).

CHQ-PF50 is a validated quality-of-life measure currently used in pediatric studies. In this measure, the parent answered questions that assessed 14 core health concepts, and resulted in 2 summary scores: one for the subject's physical well-being and another for the subject's psychosocial well-being. The transformed scores ranged from 0 to 100, with higher scores indicative of improved health.

CPRS-R is a comprehensive scale that used observer and self-report ratings to help assess ADHD and evaluate behavioral issues in children and adolescents. The CPRS-R, which was used to assess duration of effect, is a parent-rated subscale of 27 items related to ADHD symptoms and problem behaviors. Items are rated on a scale of 0 (not true at all, never, seldom) to 3 (very much true, very often, very frequent). The CPRS-R was completed at 6 AM, 6 PM, and 8 PM during the baseline visit and visit 6.

PDSS is a self-rated assessment of daytime sleepiness that was completed at screening, baseline, and visits 1 through 9. The subjects responded to 8 questions related to sleepiness using a Likert scale rating (never = 0; always = 4). Higher scores on the PDSS indicated greater levels of sleepiness.

PGA is a parent-rated variation of the CGI in which the parent or caregiver evaluates the subject's symptom severity. The PGA was completed between screening and baseline visits and again at visit 6. Responses from the PGA were dichotomized into 2 categories: "improvement" (included the responses "very much improved" and "much improved") and "no improvement" (all other responses).

PSERS is a clinician-rated scale used to assess the severity of AEs such as dullness, tiredness, listlessness, headache, stomach ache, loss of appetite, and trouble sleeping. The PSERS was completed at screening and visits 1 through 9. Severity of AEs was rated as none, mild, moderate, or severe.

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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