

## Shire Announces Updates from Phase 3 Clinical Program for Lifitegrast in Adults with Dry Eye Disease

- **OPUS-2**, a Phase 3 placebo-controlled study of lifitegrast 5.0%; results presented at the American Society of Cataract and Refractive Surgery (ASCRS) annual meeting in Boston
- **SONATA**, a Phase 3 placebo-controlled, long-term (one-year) safety study of lifitegrast 5.0%; top-line results announced

**Lexington, Mass. – April 30, 2014** – Shire plc (LSE: SHP, NASDAQ: SHPG), the global specialty biopharmaceutical company, presented study results from its pivotal Phase 3 OPUS -2 study investigating lifitegrast (5.0% ophthalmic solution) in adults with dry eye disease at the 2014 American Society of Cataract and Refractive Surgery (ASCRS) annual meeting in Boston earlier this week. In addition, today the company announces top-line results from the prospective, randomized, double-masked, placebo-controlled, long-term (one-year) Phase 3 SONATA safety study.

“These clinical trials are part of a large Phase 3 clinical program with more than 1,600 patients,” said Phil Vickers, Ph.D., Head of Research & Development at Shire. “We look forward to meeting with the FDA to discuss the totality of data for lifitegrast, which will help us determine our path forward.”

OPUS-2 study results on both co-primary endpoints and secondary assessments were presented at ASCRS earlier this week. Lifitegrast met one of the co-primary endpoints for the patient-reported symptom of improvement in dry eye compared with placebo ( $P < 0.0001$ ), but did not meet the second co-primary endpoint of the sign of inferior corneal staining ( $P = 0.6186$ ). The secondary endpoints were only descriptive in nature and were consistent with improvement in symptoms and lack of improvement in signs.

There were no ocular serious treatment-emergent adverse events (TEAEs) or drug-related serious TEAEs reported. The most commonly reported TEAEs associated with lifitegrast were dysgeusia (altered sense of taste) (16.2% vs. 0.3% for placebo), instillation site irritation (7.8% vs. 1.4% for placebo), instillation site reaction (7.0% vs. 1.1% for placebo), and visual acuity reduced (5.0% vs. 6.4% for placebo).

“Symptoms of dry eye are certainly the most common complaints that I hear from patients in my practice,” said Joseph Tauber, M.D., of the Tauber Eye Center, Kansas City, Mo., who also presented the OPUS-2 study results at ASCRS. “Patients come in seeking relief from their chronic and sometimes debilitating symptoms. It’s encouraging that potential new treatment options are being developed for dry eye disease, which affects millions of people in the U.S.”

### SONATA Top-Line Results

Top-line results from the prospective, randomized, double-masked, placebo-controlled SONATA trial indicated no ocular or drug-related serious adverse events. Discontinuations over the course of the study were 21.1% (23.1% for lifitegrast vs. 17.1% for placebo). At Day 360, analysis of the primary endpoints of ocular and non-ocular adverse events (AEs) showed that ocular AEs occurring in  $\geq 5\%$  of subjects included installation site irritation (15% vs. 4.5% for placebo), installation site reaction (13.2% vs. 1.8% for placebo), visual acuity reduced (11.4% vs. 6.3% for placebo), and dry eye (1.8% vs. 5.4%

for placebo). The most commonly reported non-ocular AE associated with lifitegrast was dysgeusia (altered sense of taste) (16.4% vs. 1.8% for placebo). Additional data and analyses will be submitted for presentation at upcoming medical meetings.

## **ABOUT OPUS-2**

OPUS-2 was a multicenter, randomized, double-masked, placebo-controlled, parallel-arm study comparing lifitegrast to placebo administered twice-daily for 84 days (12 weeks) in dry eye patients with a history of active artificial tear use within 30 days prior to screening. In addition to certain medications, key study exclusions included any ocular condition that, in the opinion of the investigator, could affect study parameters. A 14-day open-label placebo screening run-in period preceded randomization. Patients had to have an inferior corneal staining score of greater than or equal to 0.5 point in at least one eye with a Schirmer Tear Test score of greater than or equal to 1 and less than or equal to 10 mm in the same eye at Visit 1 (Day -14, Week -2) and replicate these findings in the same eye at Visit 2 (Day 0, Week 0) in order to be eligible for the study. Patients randomized into the study were not allowed to use artificial tears during the study. Overall, 718 patients were randomized at 31 U.S. sites. The study consisted of five visits over 98 days: screening visits Day -14 (Visit 1) to Day 0 (Visit 2), and treatment visits at Day 0 (Visit 2), Day 14 (Visit 3), Day 42 (Visit 4), and Day 84 (Visit 5).

## **ABOUT SONATA**

SONATA was a Phase 3, multicenter, randomized, double-masked, placebo-controlled study evaluating the safety of 5.0% lifitegrast compared to placebo administered twice-daily for 360 days (~ one year) in dry eye patients. In addition to certain medications, key study exclusions included any ocular condition that, in the opinion of the investigator, could affect study parameters. Patients had to have a visual analogue scale score greater than or equal to 40% in either symptom of eye dryness or discomfort, a corneal staining score of greater than or equal to 2.0 point in at least one region in either eye, and a Schirmer Tear Test score of greater than or equal to 1 and less than or equal to 10 mm in either eye at Visit 1 (Day -7). Confirmatory screening and baseline assessment occurred at Visit 2 (Day 0). Patients randomized into the study were not allowed to use contact lenses, or any topical ophthalmic treatments including artificial tears, steroid drops, antihistamine drops or mast cell stabilizer drops between Visits 1 and 3 (Day 14). Following completion of Visit 3 assessments, subjects were allowed elective use of contact lenses (daily disposable lenses only), and/or artificial tears (up to four times a day as needed) and/or topical ophthalmic steroids (loteprednol only), antihistamines or mast cell stabilizers. Overall, 332 patients were randomized (2:1, 5.0% lifitegrast: placebo) at 22 U.S. sites. The study consisted of seven visits over 367 days: screening visits Day -7 (Visit 1) to Day 0 (Visit 2), and treatment visits at Day 0 (Visit 2), Day 14 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 270 (Visit 6), and Day 360 (Visit 7).

## **ABOUT LIFITEGRAST**

Lifitegrast, a small-molecule integrin antagonist, was designed in order to treat dry eye disease, and is a preservative-free topical eye solution. Lifitegrast is believed to work by reducing inflammation through inhibition of lymphocyte function-associated antigen 1 (LFA-1) and preventing its binding to intercellular adhesion molecule-1 (ICAM-1) that influences T-cell activation and cytokine (protein) release. The interaction between these two proteins plays a key role in the chronic inflammation associated with dry eye. T-cells are important components of the immune system that help control the body's response to a foreign or harmful substance or stimuli.

## ABOUT DRY EYE DISEASE

As defined by the International Dry Eye Workshop in 2007, dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

### For further information please contact:

#### Investor Relations

Eric Rojas	<a href="mailto:erojas@shire.com">erojas@shire.com</a>	+1 781 482 0999
Sarah Elton-Farr	<a href="mailto:seltonfarr@shire.com">seltonfarr@shire.com</a>	+44 1256 894157
Jeff Poulton	<a href="mailto:jpoulton@shire.com">jpoulton@shire.com</a>	+1 781 482 0945

#### Media

Jessica Mann	<a href="mailto:jmann@shire.com">jmann@shire.com</a>	+44 1256 894 280
Gwen Fisher	<a href="mailto:gfisher@shire.com">gfisher@shire.com</a>	+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 and Internal Medicine and we are developing treatments for symptomatic conditions treated by specialist physicians in other targeted therapeutic areas.

[www.shire.com](http://www.shire.com)

## FORWARD - LOOKING STATEMENTS - "SAFE HARBOR" 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 and revenues from INTUNIV will become subject to generic competition starting in December 2014;
- 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, financial condition and results of operations;
- Shire conducts its own manufacturing operations for certain of its Rare Diseases products and is reliant on third party contractors to manufacture other products and to provide goods and services. Some of Shire's products or ingredients are only available from a single approved source for manufacture. Any disruption to the supply chain for any of Shire's 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 for some period of time.

- 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. Fluctuations in buying or distribution patterns by such customers can 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 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;
- Shire faces intense competition for highly qualified personnel from other companies, academic institutions, government entities and other organizations. Shire is undergoing a corporate reorganization and the consequent uncertainty could adversely impact Shire's ability to attract and/or retain the highly skilled personnel needed for Shire to meet its strategic objectives;
- failure to achieve Shire's strategic objectives with respect to the acquisition of ViroPharma Incorporated may adversely affect Shire's financial condition and 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 10-K.