January 29, 2017

Astellas and Ironwood Report Positive Top-Line Results from Phase III Linaclotide Trial for Patients with Chronic Constipation Conducted in Japan

TOKYO & CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Astellas Pharma Inc. (TSE:4503) and Ironwood Pharmaceuticals, Inc. (NASDAQ:IRWD) announced today top-line results indicating that the Phase III clinical trial of linaclotide conducted in Japan in adults with chronic constipation (CC) met its primary endpoint.

Linaclotide is approved in Japan as the first prescription treatment for adults with irritable bowel syndrome with constipation (IBS-C). Linaclotide is currently approved in the United States for the treatment of adults with IBS-C or chronic idiopathic constipation (CIC). It is also approved for adults with IBS-C or CIC in more than 30 other countries. Patients in the Phase III CC trial in Japan continue to receive open-label linaclotide for an additional 52 weeks; the blinded efficacy data coupled with these open-label safety data are expected to form the basis for regulatory review and potential approval for this indication in Japan.

"I am really pleased to receive the positive top-line results from the Phase III chronic constipation trial. If approved, Astellas expects linaclotide to provide a new therapeutic option for patients suffering from this condition, in addition to IBS-C, for which linaclotide has already obtained marketing approval in Japan," said Bernhardt G. Zeiher, M.D., President, Development at Astellas Group.

"Today's positive Phase III results for linaclotide in chronic constipation mark the ninth Phase III/IIIb clinical trial in which linaclotide has met its primary endpoints, once again demonstrating consistent results in clinical trials across two indications, evaluating multiple doses and conducted in multiple countries," said Mark Currie, Ph.D., Chief Scientific Officer and President of Research and Development at Ironwood. "We look forward to working with Astellas to support the launch of linaclotide in Japan for adults with IBS-C and to advance it for CC."

The double-blind, placebo-controlled Phase III clinical trial randomized 186 adults with CC in Japan to receive either 500 mcg of linaclotide or placebo for 4 weeks (1:1 ratio). The top-line trial results indicate that linaclotide-treated patients showed statistically significant improvement compared to placebo-treated patients for the primary endpoint, change from baseline in mean spontaneous bowel movement frequency at Week 1. The most common adverse event reported in this trial was diarrhea. All cases of diarrhea were characterized as mild or moderate in severity.

Further detailed results from the Phase III trial are expected to be presented at an upcoming scientific meeting.

INDICATIONS AND USAGE (UNITED STATES)

LINZESS (linaclotide) is indicated in adults for the treatment of both irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC).

IMPORTANT SAFETY INFORMATION (UNITED STATES)

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

LINZESS is contraindicated in patients less than 6 years of age. In nonclinical studies in neonatal mice, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration. Use of LINZESS should be avoided in patients 6 years to less than 18 years of age. The safety and effectiveness of LINZESS has not been established in patients less than 18 years of age.

Contraindications

- LINZESS is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.

- LINZESS is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

Warnings and Precautions

Pediatric Risk

- LINZESS is contraindicated in patients less than 6 years of age. The safety and effectiveness of LINZESS in patients less than 18 years of age have not been established. In neonatal mice, linaclotide increased fluid secretion as a consequence of GC-C agonism resulting in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.
- Use of LINZESS should be avoided in pediatric patients 6 to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, use of LINZESS should be avoided in pediatric patients 6 years to less than 18 years of age.

Diarrhea

- Diarrhea was the most common adverse reaction in LINZESS-treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. The incidence of diarrhea was similar in the IBS-C and CIC populations. Severe diarrhea was reported in 2% of 145 mcg and 290 mcg LINZESS-treated patients, and in < 1% of 72 mcg LINZESS-treated CIC patients. If severe diarrhea occurs, dosing should be suspended and the patient rehydrated.

Common Adverse Reactions (incidence =2% and greater than placebo)

- In IBS-C clinical trials: diarrhea (20% vs 3% placebo), abdominal pain (7% vs 5%), flatulence (4% vs 2%), headache (4% vs 3%), viral gastroenteritis (3% vs 1%) and abdominal distension (2% vs 1%).
- In CIC trials of a 145 mcg dose: diarrhea (16% vs 5% placebo), abdominal pain (7% vs 6%), flatulence (6% vs 5%), upper respiratory tract infection (5% vs 4%), sinusitis (3% vs 2%) and abdominal distension (3% vs 2%). In a CIC clinical trial of a 72 mcg dose: diarrhea (19% vs 7% placebo) and abdominal distension (2% vs < 1%).

Please see full Prescribing Information: http://www.allergan.com/assets/pdf/linzess_pi

About Linaclotide

Linaclotide is a guanylate cyclase-C (GC-C) agonist that is structurally related to the naturally occurring peptides, guanylin and uroguanylin. Linaclotide is thought to work in two ways based on nonclinical studies. Linaclotide binds to the GC-C receptor locally, within the intestinal epithelium. Activation of GC-C results in increased intestinal fluid secretion and accelerated transit and a decrease in the activity of pain-sensing nerves in the intestine. The clinical relevance of the effect on pain fibers, which is based on nonclinical studies, has not been established. Linaclotide is marketed by Ironwood and Allergan plc in the United States as LINZESS® and is indicated for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), with nearly 1.5 million unique patients in the United States having filled nearly 7 million linaclotide prescriptions since launch, according to IMS Health. Linaclotide is marketed by Allergan for the treatment of adults with moderate to severe IBS-C in Europe under the brand name CONSTELLA®, and Ironwood's partner Astellas received approval of linaclotide in Japan under the brand name LINZESS® for the treatment of adults with IBS-C. Ironwood also has partnered with AstraZeneca for development and commercialization of linaclotide in China, Hong Kong and Macau.

About Astellas

Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. We focus on Urology, Oncology, Immunology, Nephrology and Neuroscience as prioritized therapeutic areas while advancing new therapeutic areas and discovery research leveraging new technologies/modalities. We are also creating new value by combining internal capabilities and external expertise in the medical/healthcare business. Astellas is on the forefront of healthcare change to turn innovative science into value for patients. For more information, please visit our website at www.astellas.com/en.

About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (NASDAQ: IRWD) is a commercial biotechnology company focused on creating medicines that make a difference for patients, building value for our fellow shareholders, and empowering our passionate team. We are

commercializing two innovative primary care products: linaclotide, the U.S. branded prescription market leader for adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), and lesinurad, which is approved to be taken with a xanthine oxidase inhibitor (XOI) for the treatment of hyperuricemia associated with uncontrolled gout. We are also advancing a pipeline of internally and externally generated innovative product candidates in areas of significant unmet need, including uncontrolled gastroesophageal reflux disease and vascular and fibrotic diseases. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. For more information, please visit www.ironwoodpharma.com or www.twitter.com/ironwoodpharma; information that may be important to investors will be routinely posted in both these locations.

Ironwood Cautionary Notes

This press release contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including statements about the launch of linaclotide in Japan for adults with IBS-C; the basis for regulatory review and potential approval for linaclotide in Japan in adults with CC; the potential benefits of linaclotide; and disclosure of data from the Phase III trial, and the timing thereof. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include those related to the effectiveness of commercialization efforts by us and our partners; those related to preclinical and clinical development, manufacturing and formulation development; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of linaclotide; decisions by regulatory authorities; the risk that we may never get sufficient patent protection for linaclotide or that we are not able to successfully protect such patents; developments in the intellectual property landscape; challenges from and rights of competitors or potential competitors; and the risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, and in our subsequent SEC filings. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Ironwood undertakes no obligation to update these forward-looking statements.

Astellas Cautionary Notes

The safety and efficacy of the agents discussed herein are under investigation and have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for uses being investigated. Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice.

In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

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Source: Ironwood Pharmaceuticals, Inc. & Astellas Pharma Inc.