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AstraZeneca and Ironwood Report Positive Top-Line Data from Phase III IBS-C Trial Designed to Support Linaclotide Approval in China

- All primary and secondary endpoints met with statistical significance; companies expect to file for CFDA approval in early 2016 -

SHANGHAI & CAMBRIDGE, Mass.--(BUSINESS WIRE)-- AstraZeneca Pharmaceuticals Co., Ltd. and Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) announced today that top-line data demonstrate linaclotide met all primary and secondary endpoints, covering multiple abdominal and constipation symptoms, in a Phase III clinical trial of adults with irritable bowel syndrome with constipation (IBS-C). The trial was conducted primarily in China and the companies intend to file in early 2016 for China Food and Drug Administration (CFDA) approval to market linaclotide. Linaclotide is currently approved in the United States for the treatment of adults with IBS-C or chronic idiopathic constipation (CIC) and in a number of other countries for adults with IBS-C.

"If approved by the CFDA, linaclotide would be the first prescription treatment in China specifically for both male and female adults with IBS-C, which is estimated to affect at least 13 million men and women in this country," said Leon Wang, President of AstraZeneca China and Hong Kong. "The successful completion of this Phase III clinical trial confirms our belief that linaclotide may be able to help millions of these patients suffering from abdominal pain, bloating and multiple other abdominal and constipation symptoms associated with IBS-C."

"Linaclotide has now met all primary and secondary endpoints in all six of its Phase III/IIIb trials. The efficacy and safety results seen in this Phase III trial are consistent with the results of previous linaclotide pivotal studies in adults with IBS-C and with our experience in clinical practice, where nearly 700,000 unique IBS-C and CIC patients in the U.S. have filled more than 2.7 million linaclotide prescriptions since launch," said Mark Currie, Ph.D., chief scientific officer and president of research and development at Ironwood. "We are making progress toward our goal of bringing linaclotide to appropriate patients around the world, and we continue to innovate with our development and investigation of additional linaclotide indications and formulations intended to address a broad spectrum of patient needs."

Top-line data from the Phase III trial indicate linaclotide-treated patients showed statistically significant improvement compared to placebo-treated patients for both co-primary endpoints. 60.0% of linaclotide-treated patients were Abdominal Pain/Discomfort Responders, compared to 48.8% of placebo-treated patients ($p=0.001$). 31.7% of linaclotide-treated patients were IBS Degree of Relief Responders, compared to 15.4% of placebo-treated patients ($p < 0.0001$). Linaclotide-treated patients reported greater improvements in abdominal pain than placebo-treated patients: these effects were evident in the first week of treatment and continued to improve throughout the treatment period, with the greatest decreases in abdominal pain seen at week 12 of treatment (44% decrease for linaclotide compared to 34% decrease for placebo).

Statistically significant improvements were achieved in all pre-specified secondary endpoints in this trial, including abdominal pain, abdominal discomfort, bloating, straining, frequency of complete spontaneous bowel movements, frequency of spontaneous bowel movements and stool consistency.

The most common adverse event reported in linaclotide-treated patients was diarrhea (9.4% for linaclotide vs. 1.2% for placebo). Overall rates of discontinuation due to adverse events were 1.7% for linaclotide vs. 1.4% for placebo, while discontinuation due to diarrhea was 0.7% for linaclotide vs. 0.2% for placebo.

The randomized, double-blind, placebo-controlled Phase III clinical trial randomized 839 adults with IBS-C in China, Australia, Canada, New Zealand and the United States. Patients were randomized 1:1 to receive either 290mcg of linaclotide, or placebo, for 12 weeks. The co-primary endpoints of the trial were (i) 12-Week Abdominal Pain/Discomfort Responder, which is defined as a patient who has at least a 30% improvement in his/her abdominal pain or abdominal discomfort level for at least half of the weeks in the 12-week treatment period, and (ii) 12-Week IBS Degree of Relief Responder, which is defined as a patient who rates their IBS symptoms as being "considerably relieved" or "completely relieved" for at least half of the weeks in the 12-week treatment period. The primary endpoints used in this trial were similar to those previously used to support approval of linaclotide in the European Union. For comparison, results were also significant (33.7% for linaclotide-treated patients versus 17.4% for placebo-treated patients, nominal $p < 0.0001$) analyzing the data from this trial according to the endpoint from the FDA guidance on IBS (patients reporting at least a 30% reduction from baseline in abdominal pain and an increase of at least one complete spontaneous bowel movement from baseline, all in the same week for at least 6 out of 12 weeks).

Full results from the trial are expected to be submitted for presentation at an upcoming medical congress.

AstraZeneca and Ironwood are jointly responsible for the development and commercialization of linaclotide in China, with AstraZeneca primarily responsible for local operational execution. Under the terms of the collaboration, AstraZeneca made an upfront payment of $25 million to Ironwood, and the two companies will share the net profits and losses associated with linaclotide in China, with AstraZeneca carrying 55% of each until a certain specified milestone is achieved, moving to a 50/50 split thereafter. Ironwood is also eligible for $125 million in additional commercial milestone payments from AstraZeneca contingent on the achievement of certain sales targets.

About Linaclotide

Linaclotide is a guanylate cyclase‑C (GC‑C) agonist that 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 Actavis 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 700,000 unique patients in the U.S. having filled more than 2.7 million linaclotide prescriptions since launch, according to IMS Health. Linaclotide is marketed by Almirall, S.A. for the treatment of adults with moderate to severe IBS-C in Europe under the brand name CONSTELLA®. Ironwood also has partnered with Astellas Pharma Inc. for development and commercialization of linaclotide in Japan and with AstraZeneca for development and commercialization in China.

About AstraZeneca Pharmaceuticals Co. Ltd.

AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

For more information please visit: www.astrazeneca.com

About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (NASDAQ: IRWD) is focused on creating medicines that make a difference for patients, building value to earn the continued support of our fellow shareholders, and empowering our team to passionately pursue excellence. We discovered, developed and are commercializing linaclotide, which is approved in the United States and a number of other countries. Our pipeline priorities include exploring further opportunities for linaclotide, as well as leveraging our therapeutic expertise in gastrointestinal disorders and our pharmacologic expertise in guanylate cyclases to address patient needs across the upper and lower gastrointestinal tract. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. Connect with us at www.ironwoodpharma.com or on Twitter at www.twitter.com/ironwoodpharma; information that may be important to investors will be routinely posted in both these locations.

This press release contains forward looking statements. Investors are cautioned not to place undue reliance on these forward‑looking statements, which include, among other things, statements about the top-line assessment of the data from the Phase III clinical trial of linaclotide in adults with IBS-C and the plans for further analysis; the development and regulatory plans for linaclotide in China, and the timing of those decisions; the design of the Phase III trial and its impact on the results thereof; the design and possible benefits of linaclotide and its potential as a treatment for adult men and women IBS-C patients in China; IBS-C symptoms and the causes of such symptoms, as well as available treatments, prevalence and unmet need; market size, growth and opportunity, and potential demand for linaclotide in China; and the potential for Ironwood to receive sales-related milestones from AstraZeneca. 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, but are not limited to, the risk that Ironwood and AstraZeneca are unable to effectively or timely execute on the development and regulatory plan for linaclotide, or do so in a cost-effective manner; the risk that findings from the completed linaclotide clinical trials may not be predictive of the product's performance, if it is commercialized; the risk that unfavorable findings may arise from new clinical data or additional analyses of existing clinical data; those related to the efficacy, safety and tolerability of linaclotide; those related to decisions made by regulatory authorities and the timing of those decisions; the commercial potential of linaclotide in China; the risk that Ironwood and AstraZeneca may never get sufficient patent protection for linaclotide in China; those related to intellectual property rights of competitors or potential competitors; the risk that the patient population is not as presently estimated; the risks presented by future business decisions made by Ironwood, AstraZeneca and their competitors or potential competitors; and the risk that Ironwood or AstraZeneca terminates all or part of the collaboration

arrangement. Applicable risks also include those that are listed in Ironwood's Quarterly Report on Form 10‐Q for the quarter ended March 31, 2015, in addition to the risk factors that are listed from time to time in Ironwood's Annual Reports on Form 10‐K, Quarterly Reports on Form 10‐Q and any subsequent SEC filings. Neither Ironwood nor AstraZeneca undertakes any obligation to update these forward‐looking statements to reflect events or circumstances occurring after this press release. These forward‐looking statements speak only as of the date of this press release. All forward‐looking statements are qualified in their entirety by this cautionary statement.

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