

Astellas Submits New Drug Application for Linaclotide, Treatment for Irritable Bowel Syndrome with Constipation, in Japan

Tokyo, February 24, 2016 - Astellas Pharma Inc. (TSE: 4503, President and CEO: Yoshihiko Hatanaka, “Astellas”) today announced that it submitted a new drug application for a guanylate cyclase-C (GC-C) receptor agonist, linaclotide (generic name, ASP0456) for the indication of the irritable bowel syndrome with constipation (IBS-C) in adults to the Ministry of Health, Labour and Welfare in Japan. Astellas had entered into a license agreement with Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD, CEO: Peter Hecht, Ph.D., “Ironwood”) in 2009 to provide Astellas exclusive rights to develop and commercialize linaclotide in Japan.

Linaclotide is a guanylate cyclase-C (GC-C) receptor agonist. Linaclotide binds to the GC-C receptor locally, within the intestinal epithelium. Activation of GC-C receptor results in increased intestinal fluid secretion and accelerated transit, and improved visceral hypersensitivity. Linaclotide is approved for treatment of adults with IBS-C or chronic idiopathic constipation (CIC) in more than 30 countries. It is estimated that 2.9% of adults in Japan suffer from IBS-C ^{Ref}, and there are no prescription products currently approved in Japan for the treatment of this indication.

The submission is based mainly on the results obtained from the double-blind, placebo-controlled, parallel-group comparative study in Phase III study conducted in Japan in adults with IBS-C demonstrated linaclotide’s clinical efficacy and a safety profile. This study randomized 500 adults with IBS-C in Japan. Patients were randomized 1:1 to receive either 500 mcg of linaclotide or placebo for 12 weeks. The data indicates linaclotide-treated patients showed statistically significant improvement compared to placebo-treated patients for both of the two co-primary endpoints. Regarding the first primary endpoint, 34% of linaclotide-treated patients were Global Assessment of Relief of IBS Symptoms Responders, compared to 18% of placebo-treated patients ($p < 0.001$). Regarding the second primary endpoint, 35% of linaclotide-treated patients were Complete Spontaneous Bowel Movement (CSBM) Overall Responders, compared to 19% of placebo-treated patients ($p < 0.001$). Additionally, improvements were achieved in pre-specified secondary endpoints in this trial covering abdominal and constipation symptoms, including bloating and abdominal pain/discomfort. Diarrhea rates in this trial were 9.6% for linaclotide vs. 0.4% for placebo; all cases of diarrhea were characterized as mild or moderate in severity.

Upon this submission in Japan, Astellas will make the milestone payment of US\$ 15 million to Ironwood, which has no impact on Astellas' consolidated full-year business forecasts for the fiscal year ending March 31, 2016.

Astellas expects to provide an additional therapeutic option and further contribute to the treatment of IBS-C by introducing linaclotide into the Japanese market.

¹⁾ Irritable bowel syndrome (IBS) is a functional but not organic disorder which causes abdominal pain and/or discomfort with abnormal defecation including diarrhea and constipation. These gastrointestinal symptoms persist for a long period with frequent remissions and exacerbations. Abdominal pain/discomfort and abnormal defecation are often associated with various factors such as stress, which is considered to cause the increase of intestinal motility resulted from the over-activation of enteric nervous system.

^{Ref)} Kubo M, Fujiwara Y, Shiba M, Kohata Y, Yamagami H, Tanigawa T, et al. Differences between risk factors among irritable bowel syndrome subtypes in Japanese adults. *Neurogastroenterol Motil.* 2011;23:249-54.

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.

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