Ardelyx Receives FDA Approval for IBSRELA® (Tenapanor), an NHE3 Sodium Transport Inhibitor, for the Treatment of Irritable Bowel Syndrome with Constipation

September 12, 2019

Approval supported by two Phase 3 trials demonstrating a statistically significant reduction in constipation and abdominal pain in adult patients with IBS-C
Novel MOA offers a new and differentiated option for patients with IBS-C and the physicians who treat them
Discovered and developed by Ardelyx, IBSRELA represents the first-ever product approval for Ardelyx
Conference call to be held today at 4:30PM ET

FREMONT, Calif., Sept. 12, 2019 /PRNewswire/ -- Ardelyx, Inc. (NASDAQ: ARDX), a specialized biopharmaceutical company focused on developing innovative first-in-class medicines to improve treatment for people with cardiorenal diseases, today announced that the U.S. Food and Drug Administration has approved IBSRELA® (tenapanor), a 50 mg, twice daily oral pill for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults. IBSRELA is a minimally-absorbed small molecule that acts locally in the gastrointestinal (GI) tract to inhibit the sodium-hydrogen exchanger NHE3, resulting in an increase in bowel movements and a decrease in abdominal pain for IBS-C patients.

"IBSRELA has the potential to provide IBS-C patients and their doctors with a novel mechanism and an innovative approach to managing IBS-C, a highly burdensome and difficult-to-treat condition affecting more than 11 million people in the United States," commented Mike Raab, president and chief executive officer of Ardelyx. "This approval is an extremely important and rewarding milestone for Ardelyx, and represents the culmination of years of dedication to advancing our discoveries and medicines in an effective and rigorous manner. We look forward to establishing a commercial collaboration with a partner that has the capabilities to drive the successful launch and marketing of IBSRELA in this large and underserved IBS-C patient population."

Mr. Raab continued, "With the approval of IBSRELA for IBS-C, along with the successful completion of our AMPLIFY trial in hyperphosphatemia, we've delivered on two major corporate milestones in the last two weeks due to flawless execution by the remarkable and talented team at Ardelyx. With these milestones accomplished, and the PHREEDOM trial reading out in Q4, I have great confidence that we are well positioned to file our NDA for hyperphosphatemia next year with potential approval and launch in 2021. We are excited about this next chapter for Ardelyx as we begin the development of our playbook for launch and commercialization of tenapanor for hyperphosphatemia in chronic kidney disease patients on dialysis and are excited to begin sharing more of our vision in the coming months."

IBSRELA (tenapanor) Phase 3 IBS-C Program

Phase 3 Study Designs
The Phase 3 IBS-C program included two randomized, double-blind, placebo-controlled trials. The trial designs were identical through the first 12 weeks of treatment, and thereafter differed in that Trial 1 (NCT02686138) continued for an additional 14 weeks of treatment (26 weeks double-blind treatment), whereas Trial 2 (NCT02621892) included a 4-week randomized withdrawal (RW) period (12 weeks double-blind treatment). Patients who were enrolled in these trials met the Rome III criteria for IBS-C, related to abdominal pain and bowel movement frequency.

Primary Endpoint
The primary endpoint for both trials was the proportion of patients who were responders during the 12-week treatment period. A responder, as defined by the FDA, was a patient who experienced at least a 30% reduction in the weekly average abdominal pain score compared with baseline and an increase of at least 1 complete spontaneous bowel movement (CSBM) in weekly average from baseline, in the same week, for at least 6 of the first 12 treatment weeks.

Results
In both Phase 3 IBS-C trials, IBSRELA met the primary endpoint as compared with placebo (Trial 1: 37% versus 24%, IBSRELA versus placebo, respectively. Trial 2: 27% versus 19% IBSRELA versus placebo, respectively).

In Trials 1 and 2, the proportion of responders for 9 out of the first 12 weeks, including at least 3 of the last 4 weeks, was greater in IBSRELA-treated patients compared to placebo-treated patients. In addition, in Trial 1, the proportion of responders for 13 out of 26 weeks was greater in IBSRELA-treated patients compared to placebo-treated patients. In both trials, improvements from baseline in average weekly CSBMs and abdominal pain were observed by Week 1, with improvement maintained through the end of treatment.

In both studies, the most common adverse event was diarrhea (16% with IBSRELA vs 4% with placebo in Trial 1; and 15% with IBSRELA vs 2% with placebo in Trial 2), with severe diarrhea reported in 2.5% of IBSRELA-treated patients compared to 0.2% on placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. Overall discontinuation rates were low among patients treated with IBSRELA (7.6%) and placebo (0.8%) and the most common adverse reaction leading to discontinuation was diarrhea (6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients).

Indications and Usage
IBSRELA (tenapanor) is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS
IBSRELA is contraindicated in patients less than 6 years of age; in young juvenile rats, tenapanor caused death presumed to be due to dehydration. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in pediatric patients less than 18 years of age.

Contraindications

- IBSRELA is contraindicated in pediatric patients less than 6 years of age.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction

Warnings and Precautions

Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age

Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

Adverse Reactions

In the two IBS-C trials, the most common adverse reaction in IBSRELA-treated patients (incidence ≥2% and greater than in the placebo group) was diarrhea (Trial 1: 16% IBSRELA vs 4% placebo; Trial 2: 15% IBSRELA vs 2% placebo).

Please also see the full Prescribing Information, including Box Warning, for additional risk information.

About Irritable Bowel Syndrome with Constipation (IBS-C)
Irritable bowel syndrome with constipation (IBS-C) is a GI disorder in which abdominal pain is associated with constipation, and significantly affects the health and quality of life of at least 11 million people in the US. A study published in the American Journal of Gastroenterology in 2015 showed that over 50 percent of IBS-C patients rated their pain, constipation and straining as being "extremely bothersome." In the same study, GI symptoms led to an average 4.9 days of "disrupted productivity" and 0.8 days of missed work per month.

About IBSRELA for IBS-C
IBSRELA (tenapanor) is a locally acting inhibitor of the sodium/hydrogen exchanger 3 (NHE3), an antiporter expressed on the apical surface of the small intestine and colon primarily responsible for the absorption of dietary sodium. In vitro and animal studies indicate its major metabolite, M1, is not active against NHE3. By inhibiting NHE3 on the apical surface of the enterocytes, tenapanor reduces absorption of sodium from the small intestine and colon, resulting in an increase in water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency.

Tenapanor has also been shown to reduce abdominal pain by decreasing visceral hypersensitivity and by decreasing intestinal permeability in animal models. In rat model of colonic hypersensitivity, tenapanor reduced visceral hyperalgesia and normalized colonic sensory neuronal excitability.

Conference Call Information
The company will host a conference call today, September 12, 2019 at 4:30PM ET to discuss the approval of IBSRELA for the treatment of IBS-C. To participate in the conference call, please call (855) 296-9612 (toll-free) or (920) 663-6277 (toll) and reference call ID number 5897497. A webcast of the call can also be accessed by visiting the Investor page of the company's website www.ardelyx.com and will be available on the website for 60 days following the call.

About Ardelyx, Inc.
Ardelyx is focused on enhancing the lives of people with cardiorenal diseases by developing first-in-class medicines that matter. Ardelyx's cardiorenal pipeline includes the Phase 3 development of tenapanor for the treatment of hyperphosphatemia in people with CKD on dialysis, and RDX013, a potassium secretagogue program for the potential treatment of high potassium, or hyperkalemia, a problem among certain patients with kidney and/or heart disease. On September 3, 2019, the company reported positive data from AMPLIFY, a pivotal Phase 3 study investigating tenapanor in a combination with phosphate binders in patients with chronic kidney disease on dialysis whose hyperphosphatemia was not previously controlled with binders alone. The study successfully met the primary endpoint and all key secondary endpoints, including demonstrating a statistically significant mean reduction in serum phosphorus from baseline to the end of the treatment period. On September 12, 2019, Ardelyx received approval of IBSRELA (tenapanor) for the treatment of irritable bowel syndrome with constipation (IBS-C). To efficiently bring its treatments to market, Ardelyx is pursuing strategic collaborations for IBSRELA for IBS-C and tenapanor for hyperphosphatemia in certain territories. Ardelyx has established agreements with Kyowa Kirin Company Limited in Japan, Fosun Pharma in China and Knight Therapeutics in Canada. For more information, please visit http://www.ardelyx.com and connect with us on Twitter @Ardelyx.

Forward Looking Statements
To the extent that statements contained in this press release are not descriptions of historical facts regarding Ardelyx, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor of the Private Securities Reform Act of 1995, including the potential for IBSRELA in treating IBS-C patients, the potential for Ardelyx's product candidates in treating the diseases and conditions for which they are being developed, Ardelyx's ability to establish additional collaborations, including a collaboration for the commercialization of IBSRELA, Ardelyx's expectations regarding the size of the patient populations for IBSRELA and for its product candidates, Ardelyx's expected timing of its NDA filing for tenapanor for hyperphosphatemia in CKD patients on dialysis, and Ardelyx's current expectations regarding the potential commercialization of tenapanor for hyperphosphatemia. Such forward-looking statements involve substantial risks and uncertainties that could cause the development of Ardelyx's product candidates or Ardelyx's future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainties inherent in the clinical development process, the uncertainties associated with the regulatory approval process, and uncertainties in the drug commercialization process. Ardelyx undertakes no obligation to update or revise any forward-looking statements. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Ardelyx's business in general, please refer to Ardelyx's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 9, 2019, and its future current and periodic reports to be filed with the Securities and Exchange Commission.

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