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Ventrus Biosciences Announces Positive Results From Pivotal Phase 3 Trial of Diltiazem (VEN 307) in Patients With Anal Fissures

Treatment Arms Show Significant Improvement Over Placebo in Three Major Outcomes

Adverse Events Similar Between Treatment Arms and Placebo

Company to Host Conference Call and Presentation Today, May 14, at 10:00 a.m. ET

NEW YORK, May 14, 2012 (GLOBE NEWSWIRE) -- Ventrus Biosciences, Inc. (Nasdaq:VTUS) today reported positive results from its Phase 3, randomized, double-blind, placebo-controlled clinical trial of diltiazem hydrochloride cream (VEN 307) in patients with anal fissures. Ventrus' development partner, S.L.A. Pharma, has completed most of the outputs for the statistical analysis plan of the Phase 3 trial, and Ventrus is pleased to communicate the data that they have generated.

The Phase 3 study randomized 465 subjects to diltiazem hydrochloride 4% or 2% w/w cream, or placebo, applied topically three times daily (TID) for 8 weeks, followed by a 4 week blinded observation period. Both 4% and 2% diltiazem treatment arms demonstrated significant improvements compared to placebo in the primary endpoint of average of worst anal pain associated with or following defecation (pain score improvement 0.44, p=0.0108, 4%; 0.43, p=0.0134, 2%) and in the secondary endpoints of overall anal-fissure-related pain (pain score 0.36, p=0.030, 4%; 0.40, p=0.0183, 2%) and anal fissure healing (32.7%, p=0.0181, 4%; 31.2%, p=0.0359, 2%). Pain endpoints were assessed using an 11-point numerical pain rating scale (Likert-like scale).

Adverse events (AEs) were similar for the three treatment arms. Gastrointestinal Disorders were the most common. Reports of headaches were similar in the three arms (14.7% of 4% diltiazem, 12.3% of 2% diltiazem, and 14.2% of placebo). There was one serious adverse event of surgery for hemorrhoid reported in this trial. The study was conducted in 31 centers in Europe by S.L.A. Pharma, the product candidate's licensor. Ventrus holds rights to diltiazem hydrochloride cream in North America.

Based on these results, Ventrus will request a meeting with the U.S. Food and Drug Administration (FDA) to discuss the Phase 3 diltiazem study, as well as steps to move forward toward a New Drug Application (NDA). Because diltiazem is approved in oral formulations for the treatment of angina and high blood pressure, it is eligible for the FDA's 505(b)2 registration pathway. The Company is also preparing to initiate a second pivotal Phase 3 study of VEN 307 in anal fissures in the second half of 2012.

"These results mark a watershed event for Ventrus, in that they highlight the potential for VEN 307 to be a treatment of choice for anal fissures and set off a potentially transformative period for the Company," said Russell H. Ellison, M.D., M.Sc., Chairman and Chief Executive Officer of Ventrus Biosciences, Inc. "The outcome of this study exceeded our expectations, demonstrating an improvement in all three measures of efficacy — pain on defecation, average daily pain and healing — results never before achieved in a single trial of a topical drug in this disorder. We look forward to next steps in the clinical and regulatory process, and to bringing VEN 307, as expeditiously as possible, to those suffering from anal fissures."

Dr. Ellison added: "We thank our partners and colleagues at S.L.A. Pharma for conducting a high quality, well executed study, and for their timely reporting of outcomes. These results come as Ventrus prepares for near-term pivotal data from a second pipeline product, VEN 309, in hemorrhoidal disease. Combined, these product candidates may represent very significant advancements for two of the most prevalent and underserved disorders in gastroenterology."

Results in Detail

I. Study Population

The study randomized 465 subjects 1:1:1 to three treatment arms, 4% or 2% diltiazem hydrochloride cream or placebo applied topically three times daily (TID) in and around the anus for 8 weeks. To be eligible for the study subjects must have had an average baseline Numerical Rating Scale (NRS), Likert Scale, score of ≥4 for worst pain associated with or following defecation during the 7 day screening period. Baseline score for worst anal pain on defecation was the average of the last three NRS scores recorded during the 7 days prior to randomization; baseline score for the overall anal pain was the average of all recorded overall daily anal pain scores during the 7 day screening period. Subjects used a telephone Interactive Voice Response System (IVRS) daily to report pain.

There were 520 subjects screened, 465 randomized, and 440 subjects that completed the 12 week study period. Of the 25 subjects that discontinued, 15 were during the first 4 weeks (5 per arm), 9 during weeks 5-8 (4% diltiazem: 3, 2% diltiazem: 1, and placebo: 5), and 1 during weeks 9-12 in the 2% arm. Three of the subjects that discontinued during the first 4 weeks were due to an adverse event (headache, anal eczema, and pain in the anal region).

There were 465 subjects randomized to the study, 156, 154, and 155 subjects randomized to the 4% diltiazem, 2% diltiazem, and placebo arms respectively in the Intent to Treat (ITT) population as well as the Safety population. There were 402 subjects in the per-protocol population, 132, 134, and 136 to the 4% diltiazem, 2% diltiazem, and placebo arms respectively. The majority of the subjects were randomized in Romania with 309, 86 Bulgaria, 30 Germany, 17 Lithuania, 14 UK, and 9 from Spain. Mean age ranged from 42.5 to 44.2 years, with 56.6% females and 43.4% males. All subjects were Caucasian in the study except one Asian subject in the placebo arm.

II. Outcomes

The primary endpoint was change from baseline in average of worst anal pain associated with or following defecation ("worst anal pain") for Week 4 (7 treatment days preceding the Week 4 visit). The secondary endpoints included: Change from baseline in average of daily overall anal fissure (AF) -related pain ("daily overall anal pain") for each week, proportion of subjects who have complete healing of AF by Week 8, percentage of subjects achieving an average of ≥30% reduction from baseline in the NRS for worst anal pain for Week 4, and Patient Global Impression of Improvement (PGI-I) by Week 4.

All randomized subjects were included in the analysis (ITT). Missing NRS scores were baseline observation carried forward (BOCF) for all missing pain scores due to discontinuation for AE or loss of efficacy (n=4) and last observation carried forward (LOCF) for all other missing pain scores. Mean baseline NRSs were balanced across the three treatment arms (4% diltiazem: 6.40, 2% diltiazem: 6.21, and placebo: 6.38). There was no treatment-by-center interaction for the primary endpoint analysis. The primary endpoint of Week 4 change in NRS for worst anal pain was analyzed using a model that included treatment, center, mean baseline NRSs and previous failure with GTN (glycerine trinitrate).

Primary Endpoint:

Both 4% and 2% diltiazem treatment arms demonstrated statistically significant improvement over placebo for change in Week 4 NRS for worst anal pain. Reduction in pain score was 0.44 (p=0.0108) and 0.42 (p=0.0134), for 4% and 2% diltiazem, respectively. The significant response started at Week 3 for both arms and continued to Week 8, with a reduction in pain score of 0.51 (p=0.006) and 0.41 (p=0.022) for 4% and 2% respectively at Week 8. As a sensitivity analysis, BOCF was used for all missing pain data, results were essentially unchanged with reduction in pain scores at Week 4 of 0.39 (p=0.017) and 0.41 (p=0.0118), for 4% and 2% diltiazem, respectively.

Secondary Endpoints:

The secondary endpoint of overall daily AF-related anal pain for Week 4 was significant for both the 4% and 2% diltiazem arms vs. placebo with a reduction in pain score of 0.36 (p=0.030) and 0.40 (p=0.0183) respectively. Mean baseline NRS were balanced across the three treatment arms (4% diltiazem: 5.84, 2% diltiazem: 5.93, and placebo: 6.04). The significant response started at Week 2 for the 2% diltiazem arm and continued to Week 8, with a reduction in pain score of 0.63 (p=0.001) at Week 8. The significant response started at Week 4 for the 4% diltiazem arm and continued to Week 8, with a reduction in pain score of 0.55 (p=0.004) at Week 8.

Healing at Week 8 was significantly improved for both 4% and 2% diltiazem arms compared to placebo, 32.7% (p=0.0181) and 31.2% (p=0.0359) vs. 23.9%, respectively. There was no significant difference from placebo in healing at Week 4.

Subjects were classified as responders if their Week 4 reduction in worst anal pain NRS was ≥30% reduction from baseline. 56% of subjects on 4% diltiazem and 47% of subjects on placebo were classified as responders (p=0.048). There was no difference in the response rate in the 2% diltiazem and placebo.

There was no difference in the overall daily anal pain between arms for ≥30% reduction in NRS from baseline to Week 4.

The PGI-I showed a significant difference between 2% diltiazem vs. placebo at Week 4 and 8 with p=0.0106 and 0.0328 respectively. There were no significant differences in the PGI-I with 4% diltiazem and placebo.

Analgesic usage was not increased in either active treatment arm compared to placebo. The average number of days/week for analgesic use was significantly lower for weeks 1-4 for the 2% diltiazem arm vs. placebo (p=0.034).

Safety and Tolerability:

Adverse events (AEs) were similar for the three treatment arms. Gastrointestinal Disorders were the most common (4%

diltiazem: 65.4%, 2% diltiazem: 59.1%, and placebo: 54.2%). The majority of the Gastrointestinal Disorders were anal pain recorded as an AE (4% diltiazem: 42.3%, 2% diltiazem: 41.6%, and placebo: 45.2%). Reports of headaches were similar in the three arms (14.7% of 4% diltiazem, 12.3% of 2% diltiazem, and 14.2% of placebo). There were two subjects with an AE of cardiac disorder (palpitation); one in the 4% diltiazem arm and one in the placebo arm. There was one subject in the 2% diltiazem arm with an AE of hypotension.

There was one serious adverse event of surgery for hemorrhoid reported in this trial (4% diltiazem arm), which occurred during the post-treatment follow-up phase.

There was no difference in the skin irritation scores between arms.

Conference Call and Presentation

The Company is hosting a conference call and slide presentation to discuss results from the Phase 3 diltiazem (VEN 307) study today, May 14, at 10:00 a.m. Eastern Time. To participate in the call, interested parties may dial 1-888-330-6585 (Toll-Free/North America) or 1-253-237-1143 (International/Toll) and use Conference ID: 80689163 to register ten minutes before the call is scheduled to begin. The call and presentation will be broadcast live on the internet at http://www.ventrusbio.com.

The call will be archived for replay on May 14 at 1:00 p.m. ET and will remain available until May 21. The replay can be accessed at 1-855-859-2056 (Toll-Free/North America) or 1-404-537-3406 (International/Toll) using Conference ID: 80689163. An audio replay of the call will also be available on the Company's website, http://www.ventrusbio.com, for 30 days after 1:00 p.m. ET, May 14.

About Anal Fissures

Anal fissure is a tear in the lining of the anal canal. It is a common anal disorder characterized by severe anal pain, associated with or after bowel movements. The pathogenesis of anal fissure is hypothesized to be initiated by the passage of a hard fecal bolus, resulting in a split in the epithelium of the anal canal. Along with poor vascular supply of the anal epithelium, increased activity (tone) of the internal anal sphincter smooth muscle further compromises the anodermal blood supply and contributes to the pain and ischemia of the anal epithelium, perpetuating ulceration and preventing healing.

In 2010, it was estimated by SDI Health LLC that there were approximately 1.1 million office visits per year for anal fissures.

About VEN 307: Diltiazem Hydrochloride cream

Diltiazem hydrochloride is a calcium-channel blocker that has been marketed in oral formulations for the treatment of angina and high blood pressure for over two decades. Diltiazem hydrochloride cream is applied perianally to treat pain related to anal fissure. It has been shown to normalize internal anal sphincter pressure and reduce anal maximal resting pressure, or MRP, and its vasodilator activity has the potential to improve blood supply, thereby decreasing the pain associated with anal fissures.

About S.L.A. Pharma

S.L.A. Pharma is a privately held pharmaceutical company located outside Basel, Switzerland with an operations arm in the UK, which is focused solely on developing medicines for the prevention and treatment of gastrointestinal disorders including familial adenomatous polyposis, perianal Crohn's disease, opioid induced constipation, and anal fissures and fecal incontinence.

About Ventrus

Ventrus is a development stage pharmaceutical company focused on the development of late-stage prescription drugs for gastrointestinal disorders. Our lead products are: Iferanserin (VEN 309) for the topical treatment of hemorrhoidal disease, for which the first Phase 3 clinical trial began in August 2011 and has completed enrollment, and topical diltiazem (VEN 307) for the treatment of anal fissures for which the first Phase 3 trial was initiated in November 2010, and reported positive top line results in May 2012. Our product candidate portfolio also includes topical phenylephrine (VEN 308) intended to treat fecal incontinence. VEN 307 and VEN 308 are two molecules that were previously approved and marketed for other indications and that have been formulated into our in-licensed proprietary topical treatments for these new gastrointestinal indications. VEN 309 is a New Chemical Entity (NCE).

Please Note: The information provided herein contains estimates and other forward-looking statements regarding future events. Such statements are just predictions and are subject to risks and uncertainties that could cause the actual events or results to differ materially. These risks and uncertainties include, among others: the timing, cost and results of clinical trials and other development activities involving our product candidates; the unpredictability of the clinical development of our product candidates and of the duration and results of regulatory review of those candidates by the FDA and foreign regulatory authorities; the unpredictability of the size of the markets for, and market acceptance of, any of our products, including VEN

309; our anticipated capital expenditures, our estimates regarding our capital requirements, and our need for future capital; our ability to retain and hire necessary employees and to staff our operations appropriately; and the possible impairment of, or inability to obtain, intellectual property rights and the costs of obtaining such rights from third parties. The reader is referred to the documents that we file from time to time with the Securities and Exchange Commission.

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