Centocor Extends Patient Enrollment to Evaluate CNTO 1275 in Treatment of Active Crohn’s Disease

Investigational, Human Anti-IL-12, Anti-IL-23 Monoclonal Antibody Focus of Phase II Clinical Research Trial

Centocor, Inc. has extend patient enrollment for a Phase II trial to evaluate the safety and efficacy of CNTO 1275 for reducing the signs and symptoms of active Crohn’s disease (CD), a serious gastrointestinal disorder. CNTO 1275 is a human monoclonal antibody that targets interleukin 12 (IL-12) and interleukin 23 (IL-23), proteins that occur naturally in the immune system and are believed to play a role in the inflammation associated with CD.

“This study will evaluate the effect of a targeted, human anti-IL-12 monoclonal antibody on Crohn’s disease and its symptoms,” said Dennis S. Riff, MD, Medical Director, Advanced Clinical Research Institute, Anaheim, California. “We look forward to further analysis and evaluation of this therapy as a potential treatment for patients with moderate to severe Crohn’s disease.”

Patients who are eligible to participate in the 28-week study will be randomized at week 0 to one of four treatment groups to receive active drug or placebo. Subjects will be permitted to remain on certain standard CD medications, including steroids and immunomodulators, while participating in the study. Patients will be monitored through 28 weeks with an additional visit at week 54 for a final blood test.

For more information about clinical trial sites and specific study protocol, please call 1-800-624-7994.

FDA Approves Pegasys® as the First and Only Pegylated Interferon for the Treatment of Chronic Hepatitis B

Pegasys—Most Prescribed Hepatitis C Medication—Now Approved for 1.25 Million Americans with Chronic Hepatitis B

The U.S. Food and Drug Administration (FDA) has approved Pegasys (peginterferon alfa-2a) for the treatment of chronic hepatitis B (CHB). Pegasys is the first and only pegylated interferon approved for the treatment of chronic hepatitis B, including both variations of the virus—HBeAg-positive and HBeAg-negative chronic hepatitis B.

“Chronic hepatitis B infection is a serious disease that causes more than 5,000 deaths in the United States each year,” said Salvatore Badalamenti, M.D., Medical Director, Roche. “Pegasys now offers hepatitis B patients a treatment option that is taken for a fixed duration of 48 weeks with the goal of providing a lasting response after treatment is completed.”

The Centers for Disease Control estimates that 1.25 million people in the United States are chronically infected with hepatitis B. Chronic hepatitis B can lead to cirrhosis, hepatocellular carcinoma and death.

“This approval provides another important option for the treatment of hepatitis B,” said Frederick G. Thompson, President and CEO of The American Liver Foundation. “We commend Roche for its extensive research and commitment to treating people with chronic liver diseases.”

Pegasys was approved in 2002 by the FDA for use alone and in combination with Copegus® (ribavirin, USP) for the treatment of adults with chronic hepatitis C. In February 2005, Pegasys became the first and only FDA-approved therapy alone and in combination with Copegus for the treatment of chronic hepatitis C in patients coinfected with hepatitis C and HIV whose HIV is clinically stable.

Pegasys has a dual mode of action; it slows replication of the hepatitis B virus and boosts the immune system.

Acupuncture Takes on Acid Reflux: 40% Cut in Sphincter Relaxations Brings Measure of Potential Relief

Going in circles with hiatal hernia, and while H. pylori caused ulcers, did it protect against reflux? Even the U.S. National Institutes of Health doesn’t know what causes gastroesophageal reflux disease, or GERD. And NIH’s National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) says there’s an unclear relationship between GERD, heartburn and hiatal hernia (HH). Patients may have only one out of three, any two out of three, or all three.
Nevertheless, clinicians know that all three often occur together and that a variety of lifestyle changes, medication, surgery and recently approved devices and an implant are imperfect solutions.

An encounter between a Taiwanese gastroenterologist wanting to study acupuncture and an opening at the Royal Adelaide Hospital resulted in two experiments looking into how the traditional Eastern approach might affect transient lower esophageal sphincter relaxations (TLESRs). Since TLESRs are "the most important mechanism of acid reflux in normal subjects and patients with GERD," they were targeted for study.

The paper describing the study, "Inhibition of transient lower esophageal sphincter relaxations by electrical acupoint stimulation," appeared in the August issue of the American Journal of Physiology-Gastrointestinal and Liver Physiology, published by the American Physiological Society. Research was performed by Duowu Zou, Wei Hao Chen, Katsuhiko Iwakiri, Rachael Rigda, Marcus Tippett and Richard H. Holloway of the Royal Adelaide Hospital, Australia. "It was an out-of-left-field approach, without any real expectations that it might work," according to Richard H. Holloway, in whose Royal Adelaide Hospital laboratory the work was done, "but we had well-defined technology and measurements for studying GERD." The protocol utilized electrical acupoint stimulation, a high-tech type of acupuncture, with a GERD model imposed on normal subjects by inflating a balloon in their stomachs.

In two separate studies, barely perceptible stimulation was applied at the acupoint known as Neiguan on the wrist. "This reduced TLESRs by a very significant 40%—from six an hour to 3.5 an hour," Holloway said. The paper added: that the rate of TLESRs during the Neiguan acupoint stimulation “was significantly lower than that during both the baseline period without any stimulation (six per hour, with a range of five to eight), and the period of sham stimulation at the hip (six per hour; range: four to eight) with a probability value of less than 0.02.”

The paper noted that "because gastric distension is the major trigger for TLESRs, Neiguan appeared to be a more relevant site for affecting triggering of TLESRs than did Hukouau,” another gastrointestinal-related acupuncure site.

Addressing the mechanisms of action, the paper said: “Whether gastric distension triggers TLESRs through tension or stretch receptors remains controversial. Nevertheless, because the distension volume [in the experiments] was kept constant and because acupoint stimulation did not affect gastric pressure, it seems unlikely that it was acting through alterations in gastric motility. The mechanism of inhibitory effect of electric acupoint stimulation on triggering of TLESRs thus remains to be elucidated.”

From a scientific viewpoint, the entire question of how acupuncture works is still a matter of much conjecture, though some studies have suggested that opioid receptors may be involved. So after the initial findings, the Holloway team essentially repeated the experiment to test this hypothesis by seeing if the receptor antagonist naloxone would block the acupoint effect. The results were negative, “but due to the peculiarity of results in a four-way study, we can’t be sure that opioids aren’t involved,” Holloway said.

Holloway added: “What we’ve shown here is a rather interesting proof of concept, which tackles one of the approaches to acid reflux by controlling the valve that controls acid leak. If we can stop the TSLERs events, that would be a major therapeutic gain. But it’s a major leap from where we are to a real cure," he said.

The paper concluded: The efficacy of electric acupuncture in reducing the frequency of TLESRs and reflux in patients with GERD awaits further study.

FDA Approves Remicade® as First and Only Biologic to Treat Ulcerative Colitis

Approval Marks Major Treatment Breakthrough for Patients With Debilitating Disease

Centocor, Inc. has announced that Remicade® (infliximab) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ulcerative colitis (UC), making Remicade the first and only biologic approved for UC, a chronic inflammatory bowel disease (IBD).

Remicade is now indicated for reducing signs and symptoms, achieving clinical remission and mucosal (continued on page 118)
healing, and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy. This is an unprecedented milestone in the treatment of moderate-to-severe UC; to date, no therapy has ever been indicated for mucosal healing and eliminating the use of corticosteroids.

The approval of Remicade for the treatment of UC represents a major breakthrough for patients suffering from this often debilitating disease,” said William J. Sandborn, M.D., professor of medicine, Mayo Clinic College of Medicine and head of the IBD Interest Group and director of the IBD Clinical Research Unit at Mayo Medical Center. “Not only did many patients in clinical trials experience a significant reduction in the occurrence of symptom flare-ups with Remicade, some achieved clinical remission and mucosal healing as well. This is welcome news for these patients whose only option otherwise may have been surgery to remove their colons.”

Remicade’s efficacy in the treatment of IBD is well established. First approved in the United States for the treatment of Crohn’s disease (CD) in 1998, Remicade remains the only anti-tumor necrosis factor (TNF-alpha) therapy indicated for the treatment of CD. With this new approval for the treatment of ulcerative colitis, Remicade is now the only biologic indicated for the treatment of both types of inflammatory bowel diseases, CD and UC.

In addition to UC and CD, Remicade is also indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. More than 600,000 patients have been treated with Remicade worldwide. This new approval for the treatment of UC continues to demonstrate the benefit of Remicade across immune-mediated inflammatory diseases.

Could Your Pain Medications Cause Serious Injury to Your Gut?

New Awareness Campaign by National Physician Group Tackles Risk of Potentially Serious GI Injury and Bleeding from Common Pain Drugs—How You Can Protect Yourself

A new program to educate physicians and patients about the safe and appropriate use of pain medications will focus on the potentially serious gastrointestinal complications of common pain relief medications called non-steroidal anti-inflammatory drugs (NSAIDs). The American College of Gastroenterology, a national physician organization representing 9,000 digestive health specialists in clinical practice, will launch a new educational initiative, Treating Pain without the Gut Reaction: An ACG Awareness Campaign. This program will clarify for physicians and consumers alike the potentially serious complications associated with NSAIDs, including gastrointestinal injury, ulcers and related bleeding.

The American College of Gastroenterology is undertaking this important new educational initiative because many patients who regularly used COX-II agents and are now using traditional NSAIDS may have questions and are possibly unaware of potentially serious issues regarding ongoing use of NSAIDs. “Physicians need to be proactive in evaluation of the risk of NSAID-related injury for each patient and appropriately add preventive therapy when that is warranted” according to ACG President John W. Popp, Jr., M.D., FACG. He added, “The College is concerned that patients taking either selective COX II or non-selective NSAIDs frequently available over-the-counter should talk to their physician about their relative risk of injury. If patients taking COX II drugs revert to NSAIDs in significant anti-inflammatory doses, the incidence of gastrointestinal injury, ulcers and related bleeding could increase significantly.”

Educational materials targeted to physicians, and through doctors to patients, will be the cornerstone of this new program, which will feature patient education brochures and educational slide programs among a range of other educational tools. This effort is supported in part by an educational grant from TAP Pharmaceutical Products Inc. of Lake Forest, IL.

The goals of the ACG’s multi-faceted program are to introduce new scientific information regarding the prevention of NSAID-induced injury and GI bleeding and, most importantly, to clarify in the minds of physicians and consumers appropriate options for pain management as alternatives to the COX-II class of therapies.

According to independent data referenced by the American College of Gastroenterology, traditional NSAIDs (such as aspirin, ibuprofen, and naproxen
sodium) when taken routinely by patients for relief of chronic pain pose significant risk of gastrointestinal injuries, which can occur without symptoms.

In recent years, many patients with arthritis or other conditions causing chronic pain have been treated with the COX-II class of agents (e.g., Vioxx®, Celebrex® and Bextra®), which have offered relief and apparent reduced risks of ulcers and GI bleeding, but recent reports raise significant concerns that these agents could be related to cardiovascular complications. Drug manufacturers this year voluntarily removed two COX-II drugs from the market, Vioxx® and Bextra. This spring U.S. Food & Drug Administration (FDA) required manufacturers of other prescription and over-the-counter pain medications, including COX-II Celebrex®, to include new warnings on their labels about potential cardiovascular risks while including more specific information about gastrointestinal adverse events.

**More Information About Health Concerns over NSAIDs for Analgesia and Pain Relief**

Gastrointestinal injury, ulcers and related bleeding are serious health matters that often strike patients by surprise, including those with or without any past symptoms or underlying digestive conditions. According to the American College of Gastroenterology, gastroenterologists are frequently called upon to see such patients in the emergency room setting, to identify and if possible to stop the bleeding, which if untreated, potentially can be fatal.

Historically, use of NSAIDs, including common products such as aspirin, ibuprofen and naproxen sodium, particularly when taken regularly by patients with arthritis or other conditions causing chronic pain, have been associated with ulcers which could lead to GI bleeding. The risk is related to the anti-inflammatory dose and when the new class of drugs, called COX-IIs such as Vioxx® and Celebrex®, came onto the market many patients who were regular users of NSAIDs for analgesia or pain relief, were advised by their physicians to switch to the COX-II products based on the premise that they could achieve equivalent benefits with less gastrointestinal risk than traditional NSAIDs.

Clinical studies subsequently confirmed that these newer compounds had a lower incidence of gastrointestinal bleeding. Recent scientific findings, underscored in communications from the FDA, have challenged some of these COX-II compounds, not with respect to claims of reduced risks of ulcers and GI bleeding, but because of data relating to potentially increased cardiovascular complications, including heart attack and stroke.

**Options for Pain Management in Light of NSAIDs Risks**

Physicians can choose to recommend the use of acetaminophen for patients needing analgesia or relief of chronic pain, and while this agent is believed to be relatively safe, patients will need to consult with their physicians to determine if there are any limitations or contraindications for this medication, given the patients age, health history, or use of tobacco or alcohol.

There are data from randomized controlled trials (RCTs) that misoprostol co-therapy will provide some gastric protection to those who continue to take NSAIDs. While there are no large RCTs to address whether anti-secretory drugs will reduce ulcers and related GI bleeding, they are useful for healing ulcers and many point to data that is believed to support co-therapy with acid suppressives, such as a proton pump inhibitor (omeprazole, lansoprazole, rabeprazole, esomeprazole or pantoprazole), which is likely to reduce risk.

According to ACG’s David A. Johnson, M.D., FACG, “There is significant evidence that anti-secretory treatment (PPIs) can help in the prevention of upper GI ulcer or ulcer relapse in chronic NSAID users. The caveat here is that while such ulcers might be considered as a surrogate marker for other complications, such as GI bleeding, outcome studies with PPIs have not yet been done to demonstrate efficacy in preventing GI bleeding.” Dr. Johnson added, “Nevertheless, in light of the difficulty in performing such studies, FDA and worldwide regulatory agencies have approved PPI therapies to reduce the risk of developing NSAID ulcers.”