Pharmacokinetic and Pharmacodynamic Response to a 6-Month Hydron® Octreotide Implant in Patients with Acromegaly

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Introduction:

Indevus Pharmaceuticals, Inc. (33 Hayden Avenue, Lexington, MA 02421) has developed a soft, flexible, subcutaneous implant that allows the continuous release of octreotide acetate for six months for the treatment of acromegaly. The implant is based on the patented Hydron® hydrogel polymer drug delivery technology, which is also utilized in Indevus' currently approved and marketed products Supprelin LA® (for treatment of precocious puberty) and Vantas® (for treatment of prostate cancer). The implant provides a constant six-month delivery of Octreotide acetate, a potent and long-acting octapeptide that mimics the natural hormone somatostatin to block production of growth hormone (GH) and other factors.

Background:

Acromegaly is a chronic hormonal disorder caused by excess production of GH, usually due to the presence of benign pituitary tumors. Excess GH stimulates the production of other hormones, such as insulin-like growth factor -1 (IGF-1), resulting in abnormal bone and tissue growth, joint pain, sexual irregularities and other physiological complications. If left untreated, acromegaly leads to other conditions such as vascular disease, stroke, heart attacks, lung disorders, and certain cancers.

A number of treatment options exist for acromegaly, including transsphenoidal surgery, radiation, life-style changes to mitigate complicating factors, and pharmacotherapy. Among the various pharmacotherapy options, the most frequently used treatment employs Novartis' Sandostatin®, a short-acting subcutaneous Octreotide injection, and a longer acting depot injection, Sandostatin LAR®. Sandostatin LAR® is a slow release formulation of octreotide encapsulated in biodegradable polymer microspheres that requires monthly intramuscular injections.

Methods:

A six-month phase I / II proof-of-concept clinical study evaluating the pharmacokinetics, efficacy, safety, and drug release characteristics of the Hydron® Octreotide implant in 11 acromegaly patients was completed in 2004. A second six-month study, initiated in September 2006, examined pharmacokinetic/ pharmacodynamic (PK/PD) parameters, GH/IGF-1 levels, and safety in 34 patients with acromegaly who had demonstrated a full or partial GH and IGF-1 response to prior octreotide therapy.

Results:

Results from the 2004 trial demonstrated reductions in GH and IGF-1 levels in the blood of these patients for six months. Side effects were generally mild, and included diarrhea, low blood sugar, and implant site reactions; no patient discontinued treatment due to side effects. In the 2006 trial, approximately half of the patients had a baseline growth hormone level of <5 ng/mL upon entry into the study, indicating that prior octreotide injections were providing adequate control. The Hydron® Octreotide implant successfully maintained GH at this level in 94% of patients. Approximately 60% of patients in the study with normalized GH also achieved normal, age-adjusted IGF-1 concentrations. The remaining patients entered the trial with baseline GH levels >5 ng/mL; 59% of these patients achieved GH suppression to <5 ng/mL, while 35% achieved suppression to <2.5 ng/mL. All enrolled patients completed the six month trial with no serious or severe adverse events reported. Octreotide and corresponding GH concentrations from this study are illustrated in Figure 1.

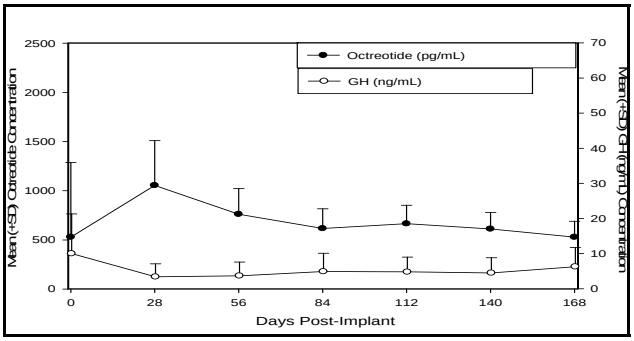

Figure 1. Average (+SD) 6-Month Serum Concentration vs. Time Profile for Octreotide and GH at Pre-Treatment and Months 1, 2, 3, 4, 5, and 6.

Conclusions:

The PK/PD data obtained from these clinical studies demonstrate that the Hydron® Octreotide implant is capable of achieving continuous GH suppression to 5 ng/mL or less for six months in patients with acromegaly. These results suggest an improvement over currently utilized daily and monthly formulations of octreotide. International Phase III clinical trials (including US sites) are underway.