Chemistry & Biology, Vol. 10, 371–372, May, 2003, ©2003 Elsevier Science Ltd. All rights reserved. DOI 10.1016/S1074-5521(03)00106-6

Innovations

Neurocrine Biosciences, Inc.

Soporific Science

We spend approximately one-third of our lives sleeping, yet a definite understanding of the purpose of sleep remains elusive. Sleep is no doubt critical to a person's well being, whether or not the detailed mechanisms linking health and sleep are known. Unfortunately, 51% of the U.S. adult population complains of insomnia, according to the National Sleep Foundation's 2001 Sleep in America Poll. In fact, nearly three out of ten Americans (29%) say they experience insomnia every night or almost every night. And while there is a range of available sleep aids for insomnia sufferers, many come with a range of problems. From over-the-counter sleeping pills to prescription drugs, often the medicines simply do not induce sleep, or if sleep is successfully provided, the next-day residual effects are frequently burdensome.

Those suffering from transient or chronic insomnia can hope for maintained sleep without next-day impairment provided by indiplon, a new compound with an anticipated approval from the Food and Drug Administration (FDA) after submission in late 2003. Produced by Neurocrine Biosciences, this novel therapeutic has successfully advanced through phase I and II clinical trials, and since November 2001 it has been progressing through phase III trials.

Indiplon is a nonbenzodiazipine sleep-promoting drug that enhances the action of the inhibitory neurotransmitter GABA. To achieve this, indiplon acts as an agonist at specific sites on the GABA-A receptor. Similar to the current sleep aids Ambien and Sonata, indiplon shows specific binding to BZ1 or Alpha1 subtypes of the GABA-A receptor and is therefore different from the classical sedative hypnotic drugs known as benzodiazepines, which do not discriminate between receptor subtypes. However, the specific binding of indiplon is much more potent for this ligand, with binding affinities 10 and 50 times greater than Ambien and Sonata, respectively. It is this receptor specificity that is thought to minimize the unwanted side effects associated with the benzodiazepine compounds.

In order to address all forms of sleeplessness—sleep initiation, night awakenings, and total sleep maintenance—Neurocrine has developed two formulations of indiplon, an immediate release (IR) formulation and a modified release (MR) formulation. Since indiplon has a short half-life, it is rapidly cleared from the bloodstream and will theoretically not impair a patient the next day. This scenario works well for those having trouble falling asleep. However, for those who awake after only a few hours, the modified release form provides the initial dose followed by another dose four hours later. This timed-release protocol has been shown to be effective for maintaining sleep throughout the night in phase II patients. Another phase II study in which the drug was administered in the middle of the night showed that there was no next-day residual sedative effect when the subjects were awakened four hours after dosing, while both Ambien (nonbenzodiazepine) and zoplicone (benzodiazepine), which have longer half-lives, showed significant sedative effects.

51% of the U.S. adult population complains of insomnia, according to the National Sleep Foundation's 2001 Sleep in America Poll.

In sleep laboratories under well-controlled conditions, a phase II double-blind placebo study was initiated using a polysomnography, which measures the time to sleep, the duration of sleep, sleep efficiency, and the number of awakenings during the night. These data were collected to find a suitable dose of indiplon to utilize in phase III clinical studies. There was a clear dose response on all parameters, and all doses significantly improved the latency to persistent sleep, the number of awakenings, and the number of patients sleeping longer than seven hours. For these titration studies, no next-day residual sedation effects were found with indiplon IR or MR, according to tests such as the Digit Symbol Substitution Test, Symbol Copy Test, and Visual Analog Scale of Sleepiness, as well as the patient's own assessment.

Indiplon is the lead clinical development for Neurocrine Biosciences, Inc. in San Diego, CA. Neurocrine will be conducting five phase III clinical trials with indiplon-IR as well as three phase III trials with indiplon-MR administered to approximately 3500 patients overall. These trials will support market registration of indiplon for short-term and long-term treatment in adult and elderly patients with primary (chronic) or transient insomnia. The clinical program for indiplon will be one of the largest and most comprehensive evaluations of a therapeutic agent for insomnia, encompassing well over 5000 patients and addressing the multiple needs of patients who suffer with insomnia.

Founded in 1992 by Wylie Vale, Ph.D. and Lawrence Steinman, MD, Neurocrine focuses primarily on small molecule drug discovery and development for treatment of neurological and endocrine system-related diseases and disorders. In addition to insomnia, Neurocrine's current projects involve therapeutics for anxiety, depression, malignant brain tumors and peripheral cancers, diabetes mellitus, multiple sclerosis, irritable bowel syndrome, eating disorders, pain, prostate cancer, obesity, and female health disorders. With its 250 employees, the company has sixteen programs in

various stages of research and development, including five in clinical development.

According to published reports, the phase I and II trials for indiplon proved to be flawless. With such a display of potential, indiplon did not go unnoticed. In December 2002, 13 months after the start of the phase III trials for indiplon, Neurocrine announced a deal worth up to $400 million to share rights of indiplon with Pfizer, the world's largest pharmaceutical company. Pfizer agreed to pay Neurocrine $100 million upfront and up to $300 million in milestone payments in return for exclusive rights to distribute the sleeping pill outside the United States and shared rights in the more lucrative U.S. market.

This deal was one of the largest in 2002 between a biotech and a pharmaceutical company. According to Michael King of Banc of America Securities, indiplon could reach $700 million in sales by 2007, about three years after its anticipated FDA approval in late 2004. "Big pharma would like to do more deals like this," said King, "but there aren't too many exciting products out there to license. Neurocrine was one of the last really good ones around, and they could have had their pick of anyone they wanted." (San Diego Union-Tribune, December 20, 2002).

The expertise of Neurocrine's two founders furnished the company with a strong 2-fold research platform. Dr. Wylie Vale and his colleagues at the Salk Institute were the first to identify and sequence the corticotropin releasing factor (CRF), a neurotransmitter in the brain, which plays a critical role in coordinating the body's overall responses to stress. Early phase I studies have shown that CRF receptor antagonist compounds for the treatment of depression and anxiety are rapidly absorbed with no apparent safety issues to preclude clinical trial advancement. Additional clinical indications for CRF1 receptor antagonists include treatment for irritable bowel syndrome, inflammatory pain, stroke, and other neurodegenerative diseases.

The second thrust of Neurocrine's research was established by Dr. Lawrence Steinman of the Stanford University School of Medicine. Steinman's expertise encompasses basic and clinical biology of immunological diseases of the central nervous system, with a focus on understanding the mechanism of action of the altered peptide ligand (APL) approach for multiple sclerosis and other autoimmune diseases such as type I juvenile diabetes. Progress is continuing through phase II clinical trials in both the multiple sclerosis and diabetes compounds.

Of course, Neurocrine's hope would be that more of their researched therapeutics follow a clinical trials path like that of indiplon. A patent for indiplon and the use of indiplon was issued in June, 2002: U.S. Patent No. 6,544,621. In early April of 2003, Neurocrine announced they had received the issuance of U.S. Patent No. 6,544,999 covering a stable polymorph of indiplon. This patent will provide Neurocrine with patent protection for this crystalline form of indiplon. With further patents to come, this potential insomnia compound will be protected for 17 years on many fronts. As part of the collaboration with Pfizer, a 200-person sales force will be established to reach psychiatrists and sleep specialists. Once the NDA (New Drug Application) is submitted, this marketing force will promote the antidepressant Zoloft to U.S. psychiatrists. With this approach, Neurocrine will establish a relationship with psychiatrists prior to the anticipated launch of indiplon, after which Neurocrine will copromote indiplon with Pfizer.

"The events of 2002 were significant milestones for Neurocrine, and as a result the company is moving closer to realizing our strategic objective of becoming a fully integrated pharmaceutical company," reported Paul Hawran, Executive Vice President and Chief Financial Officer for Neurocrine Biosciences in a PR Wire report of February, 2003. No doubt, the progress of indiplon has helped Neurocrine realize some of its goals and is a glimmer of hope for the innovative but often financially tenuous biotech companies.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

Nicole Ballew is a freelance science writer based in Lebanon, NH (nballew@hotmail.com).