**Lacosamide (ADD 234037, Harkoseride, SPM 927)**
**Journey from Laboratory Bench to Clinic**

*New Compound Poised for Use in Treating Epilepsy*

In the 1990s, Harold Kohn, Ph.D, then at the University of Houston, synthesized a compound that was later to be known as Harkoseride then SPM 927 and finally lacosamide. Dr. Kohn was originally interested in understanding mechanisms associated with the actions of the vitamin, biotin that is a very simple molecule with an embedded acyclic imidazolidinone group. After working with these molecules he observed a common structural component common to certain other central nervous system (CNS) acting agents. He hypothesized that certain modifications combined with alanine and later serine might have favorable action on neuronal circuitry. Next, he sought and found a partner at the National Institutes of Health (NIH) to evaluate and test his drug. As a result, a series of compounds were submitted to the NIH's Anticonvulsant Screening Program (ASP). Through the ASP, Harkoseride was identified in 1994 as a promising agent and subsequently advanced through preclinical pharmacology testing. The ASP also played a critical role in aiding the academic inventor in establishing the strategic partnerships required for more advanced development. These included the Harris FRC Corporation and the current developer, Schwarz Pharma AG.

Harkoseride takes its name in part because it is structurally related to serine, a naturally occurring amino acid. In multicenter phase II trials using harkoseride, there was a statistical reduction in seizure frequency. The drug was also well tolerated by study participants, nearly 500 patients in all, with partial seizures resistant to other AED treatments. The most common side effects during the trials has been dizziness, fatigue, nausea, and ataxia. Now, a decade later Schwarz has just announced the start of a large-scale Phase III clinical trial to further evaluate its efficacy and safety. More than 90% of patients who completed the initial trial entered the follow-up trial. Harkoseride (SPM 927) has also been found to be effective in several models of pain. Clinical testing is also underway for this indication.

This compound's remarkable ten-year journey to reach the Phase III milestone stands as a successful example of a successful translational research approach being supported by the NIH. The concept of translational science can be viewed as applying ideas, insights, and discoveries, generated through basic scientific inquiry, to the processes involved in the developmental and regulatory march towards new treatment and/or prevention of human disease. The National Institute of Neurological Disorders and Stroke (NINDS) and other components of the NIH are currently providing funding for a growing number of institutions and individual investigators as part of the agency's overall commitment to an established set of interactive processes better known as "translational research".

The discovery and selection of this compound was accomplished by establishing a close partnership involving different expertise including a dedicated chemistry effort, quality pharmacology and validation, structure activity assessments and business planning. We screened several in a series of both inactive and active compounds, finally choosing

harkoseride as the best candidate to put forth into human testing. Harkoseride produced an excellent preclinical profile from the battery of *in vivo* and *in vitro* models we employ. This is critically important to assure the maximum optimization of candidate compounds being proposed for human testing. Using the ASP's combination of both mechanistic and non-mechanistic models has been the key component in selection of candidates that have the best chance of completing the rigors of clinical testing and ultimately reaching our patients. This particular compound is just one example of how we are working to translate basic science and early developmental success into therapeutic realities.

While we must acknowledge that less than 60% of Phase III compounds ever reach the marketplace, we have long believed that this compound has an excellent chance to one day help relieve the suffering of 1000's of patients with epilepsy.

Contributed by James P. Stables, NINDS/NIH ASP Program Director