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TOP 10 PIPELINES

With the recession's ripple effects far-reaching, pharma and biotech explore new ways to innovate, p.16

Novel approaches for CNS drugs

By Michael D. Christel

Although most of Eli Lilly and Co.'s recent headlines center around the company's high-profile acquisition of the biotech **ImClone Systems** Inc., the drugmaker that launched Prozac continues to develop potentially novel neuroscience compounds. According to executives, Lilly has 13 new chemical entities being tested that target disorders of the central nervous system, including a pair of promising late-stage compounds – the monoclonal antibody **LY2062430** and the gamma secretase inhibitor **LY450139** – for Alzheimer's disease.

Executives have even higher hopes for Lilly's Phase II candidate for schizophrenia, **LY2140023**, a metabotropic glutamate receptor agonist. If successful, the drug would be the first non-dopamine or serotonin-blocking compound on the market for schizophrenia. These projects, combined with late-stage candidates in multiple sclerosis and depression, and investigational medicines in development for migraine and sleep deprivation, earns Lilly recognition from *R&D Directions* editors for the industry's Best Central Nervous System Pipeline.

"In terms of CNS, we're back," says Steven Paul, M.D., executive VP for science and technology and president of Lilly Research Laboratories (lilly.com). "The [pipeline] is pretty balanced across the board. The molecules are either past proof of concept or we have data, or are in Phase II, or, ideally, in many of ours, are in Phase III."

According to Dr. Paul, Lilly focuses its neuroscience research in three areas. The psychosis segment has historically been the company's staple with Prozac and other big sellers **Zyprexa**, **Cymbalta**, and **Strattera**. Lilly's other two areas of emphasis are neurodegeneration and pain.

"Given some of the challenges with cox-2 inhibitors, we've really exploited our glutamate receptor platform to come up with new pain medicines that look very interesting, both for migraine pain as well as other types of neuropathic and non-neuropathic pain," Dr. Paul told *R&D Directions*.

Nevertheless, Alzheimer's disease, with a growing patient population and significant unmet need, remains a crucial target for Lilly and other drugmakers. The condition has been traditionally frustrating and difficult to diagnose and, despite considerable research being

done in the field, setbacks have been numerous.

Dr. Paul says Lilly is the only company with two Phase III molecules for Alzheimer's disease in development. According to Dr. Paul, enrollment in the Phase III Identity trial for LY450139 is ahead of schedule. Two Phase III trials for the drug were launched in 2008. Previous Phase II data revealed that LY450139 has the potential to slow the rate of the formation of amyloid beta – the hallmark of Alzheimer's disease pathology – and slow down disease progression.

LY2062430, which will enter Phase III in the first half of this year, is intended to decrease the amount of soluble amyloid beta in the brain, making it less prone to aggregate and form amyloid plaques. Phase II results, disclosed last year, showed that the antibody was safe and had a favorable effect on biomarkers, suggesting the medicine is hitting its target.

"They're very exciting molecules, potentially disease-modifying therapies," Dr. Paul says. "Those really well-documented anti-amyloid therapies are starting to get into the phases of development where you determine whether they work. You need to wait about two years until you see whether these work or not."

LY2140023 may provide a breakthrough for schizophrenia after a Phase II study published in September 2007 demonstrated, for the first time in humans, that an mGlu2/3 agonist has antipsychotic activity. "This is a molecule that works through a completely different mechanism for treating psychosis, and we established proof of concept in a clinical study in patients with schizophrenia," Dr. Paul says. "This is a molecule that doesn't work like any of the traditional molecules, which pretty much all block dopamine or serotonin receptors. This has no activity at dopamine or serotonin receptors."

R&D TIDBITS

- LY2624803 is in Phase II trials for insomnia. The drug, obtained in Lilly's 2007 acquisition of Hypnion Inc., promotes sleep onset as well as sleep maintenance. According to executives, the molecule does not work like the traditional benzodiazepines, but instead operates through histamine and serotonin receptors.
- The company is developing drucotide, a synthetic peptide for the treatment of secondary progressive multiple sclerosis, with BioMS Medical Corp. The Phase III compound was given fast-track status by FDA in September 2008.
- Thirteen of the 22 projects in late-stage development are biologics.



For the complete listing of compounds in Lilly's pipeline, visit *R&D Directions* at Pharmalive.com.