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Product Discovery & Development

Arcion's improved (noci)reception

By Michael Flanagan
Senior Writer

Arcion Therapeutics Inc. is hoping to improve on both the efficacy and safety of systemic therapies for diabetic neuropathy by combining a topical approach with a screening test to identify patients with increased nociceptor expression. The company reported Phase IIb data last month suggesting its ARC-4558 gel was effective in providing pain relief for a prospectively defined subset of patients with increased nociceptor function.

"There are a number of drugs now approved for diabetic neuropathy, but there remains a large unmet need given that patients often have problems with the side effects on top of the fact that efficacy is highly uneven," said President and CEO James Campbell. "A lot of patients who are responders still have a fair amount of pain."

Oral drugs commonly prescribed for diabetic neuropathy include Lyrica pregabalin, a GABA receptor agonist from **Pfizer Inc.**, and Cymbalta duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) from **Eli Lilly and Co.**, as well as opiates.

Side effects on Lyrica's label include dizziness, somnolence, dry mouth and peripheral edema, as well as more serious risks such as angioedema, hypersensitivity reactions, seizures and suicidality. Cymbalta carries warnings about nausea, somnolence, insomnia and dizziness, as well as a possible risk of hepatotoxicity, orthostatic hypotension, abnormal bleeding, mania and seizures.

Opioids are associated with nausea, drowsiness and the risk of dependence.

Arcion's ARC-4558 is a 0.1% gel formulation of clonidine, a direct-acting adrenergic receptor alpha 2 (ADRA2) agonist. The gel is designed to deliver the agent directly through the skin, "where it acts on the terminal end of irritable nociceptors or hyperactive pain fibers" to provide pain relief, Campbell said.

"Our idea is to avoid the side effects associated with systemic exposure while also opening the therapeutic window by knocking down the pain generators in the periphery, particularly in the skin," Campbell said. Topically targeting abnormally sensitive pain fibers "provides a new way of controlling chronic pain, and should allow for a better safety and tolerability profile with efficacy that is at least on par with the marketed agents," he said.

Compared to marketed drugs for diabetic neuropathy, said COO Kerrie Brady, ARC-4558 has potential for "use as a standalone first-line agent or as an add-on for patients who are currently stabilized on oral medication but not getting sufficient pain relief."

The initial clinical work with ARC-4558 was conducted by **Curatek Pharmaceuticals L.P.**, which moved it into a Phase III trial in patients with post-herpetic neuralgia and diabetic neuropathy in 2000. The compound did not meet the primary endpoint of pain relief from baseline and Curatek later shifted its focus to the dermatology space. Arcion purchased the assets in 2006 for undisclosed terms.

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**James Campbell,
Arcion Therapeutics**

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“At the time, though, there was not a very good understanding about how to design neuropathic pain trials or how to interpret the results, but after I went back and did some data mining there was a clear positive signal there,” said Campbell.

Arcion believes it can amplify this efficacy signal by focusing on a subset of patients. “What has begun to emerge in the neuropathic pain field is the concept that the disease involves two phenotypes. One involves patients who experience pain originating in the nociceptors or pain fibers that are expressed in the skin, in which case a topical therapy makes sense,” he said.

“The other extreme involves pain signaling that has shifted upstream to more proximal levels of the peripheral nervous system, such as the spinal cord, or in some cases even the central nervous system,” in which case a systemic therapy is likely to be more effective, Campbell added.

Arcion’s hypothesis is that ARC-4558’s success hinges on identifying patients with higher levels of nociceptor expression in the skin.

To identify these patients, the company devised a test that involves putting a metered amount of OTC capsaicin cream on a distal part of the leg, covering it for 30 minutes, and then asking a patient to rate the pain on a 0-10 scale.

“The key thing about the capsaicin test is that it stimulates the same type of pain fibers in the skin that we are looking for clonidine to act on. Other tests involving skin pricks, vibrations or reflex stimuli

involve other receptors in addition to the pain receptors,” said Brady.

Arcion designed a Phase IIb trial to both validate the screening tool and test the hypothesis that ARC-4558 would be more effective in patients with preserved nociceptor function in the skin. The study compared ARC-4558 vs. placebo gel given as either monotherapy or as add-on to stable oral therapy in 180 patients with moderate to severe diabetic neuropathy.

Campbell said the data showed “a nice correlation” between a patient’s ratings on the pain scale and the level of skin nociceptor expression. The results showed roughly 50% of patients had some response to the capsaicin stimulus test, he added.

Regarding efficacy, the study’s statistical analysis plan was prospectively designed so that if there was a positive relationship between pain relief and skin innervation, patients with no nociceptor expression were analyzed separately from patients with nociceptor expression.

Thus, while ARC-4558 only showed a trend towards pain relief vs. placebo in the 180-patient intent to treat population ($p=0.069$), the compound was significantly more effective in patients with nociceptor expression ($p<0.05$). In addition, the level of pain relief increased in patients with higher levels of nociceptor expression ($p<0.005$).

“In other words, we established where it does work and also where it does not work,” Campbell said.

Arcion also reported that adverse events were higher in the placebo arm, and no serious adverse events were re-

lated to ARC-4558.

Systemic formulations of clonidine have been used for decades for a variety of indications, including alcohol and narcotic withdrawal, attention deficit hyperactivity disorder (ADHD), hot flashes associated with menopause and hypertension. It is also approved as an oral tablet and transdermal patch to treat hypertension.

Campbell noted that pharmacokinetic studies have shown that blood levels of clonidine produced by ARC-4558 “are at or below the detection limit, and are far below the threshold used for treating hypertension,” which is supported by results from pharmacokinetic studies showing the compound has no impact on blood pressure.

The company closed on a \$9 million series A round in early 2008 and raised another \$6 million in convertible debt over the last year. Campbell said the company will look to raise an undisclosed amount in a series B round, partner the program or entertain offers to sell the program before moving ARC-4558 into Phase III testing, which is slated for 4Q10 or 1Q11.

The Phase III program will enroll 200-500 patients with increased levels of nociceptor expression identified using the same capsaicin screening test.

COMPANIES AND INSTITUTIONS MENTIONED

Arcion Therapeutics Inc., Baltimore, Md.

Curatek Pharmaceuticals L.P., Buffalo Grove, Ill.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.