

Press Release



Pharmaleads announces the inclusion of the first patient in Phase IIa study of oral PL37 for pain in diabetic neuropathy

World premiere for Dual Enkephalinase Inhibitors (DENKIs), a new class of analgesics and first novel concept for decades in the treatment of chronic pain

Paris, 22 April 2015 – Pharmaleads, a company specialising in the discovery and early-stage development of small molecule inhibitors of metalloproteases for the treatment of severe pain, announces today the inclusion of the first patient in Phase IIa clinical study of oral PL37 in diabetic neuropathy.

This Phase II clinical study follows a major Phase I programme which demonstrated the tolerance and safety of PL37 in 136 healthy volunteers. This first Phase II study during which patients will receive PL37, the most advanced molecule in this new class of analgesics, is a world premiere for Dual Enkephalinase Inhibitors (DENKIs).

PL37 is the first DENKI to reach Phase IIa. DENKIs target specifically the nociceptors (receptors reacting to painful stimuli) located on peripheral nerve endings. They increase the concentrations of enkephalins (endogenous morphine) only where they are produced in large concentrations in response to a painful stimulus. In the absence of PL37, enkephalins are very rapidly inactivated by two enzymes called enkephalinases. By inhibiting these enkephalinases, DENKIs induce lasting analgesic effects, as potent as those of morphine but without its side effects.

Clinical study

This on-going clinical study will recruit 108 patients with diabetic neuropathy and poor pain relief provided by pregabalin or gabapentin, the most commonly prescribed treatments for neuropathic pain. Unfortunately, none of the treatments currently available to treat

neuropathic pain are satisfactory. These drugs are truly effective in only less than a quarter of patients, and they are associated with major side effects (nausea, dizziness, somnolence), which reduce their therapeutic range.

This Phase IIa study aims to demonstrate the superiority of PL37 versus placebo, when administered in combination with the standard treatment for diabetic neuropathy. This superiority is based on a remarkable synergy observed between PL37 and pregabalin or gabapentin. The difference between PL37 and placebo will be based on changes in the overall pain score evaluated by the patient during the treatment.

A total of 12 study centres are currently active, or will be within the next few weeks, in hospitals in the UK, and 6 to 10 others will open before the summer in the diabetology department of university teaching hospitals in France.

According to Michel Wurm, MD, Corporate Development Director at Pharmaleads, « *One of the strengths of this study lies in the remarkable synergy (factor 6), demonstrated in rodents when PL37 is combined with gabapentin or pregabalin. This synergy is expected to provide a highly significant clinical benefit in this Phase IIa study when PL37 is added to the unsatisfactory previous treatment* ».

« *Neuropathic pain is more intense, more lasting and more difficult to treat than other types of pain because it does not respond to standard analgesics or morphine. Neuropathic pain is not just a symptom, it is a disease that needs to be controlled. The development of new molecules, such as DENKIS, offers a great hope for patients* », comments Prof. Didier Bouhassira, neurologist at the Pain Evaluation and Treatment Centre of Hôpital Ambroise Paré (Boulogne-Billancourt, France), and Past-President of SFETD (*Société Française d'Étude et de Traitement de la Douleur*).

Neuropathic pain

Neuropathic pain (NP) is the consequence of nerve damage or dysfunction. These lesions can be caused by numerous conditions affecting the peripheral nervous system, e.g. diabetes, postherpetic neuralgia, postsurgical neuropathy, or neuropathy induced by certain drugs such as those used for cancer or HIV infections. Neuropathy is associated with pain triggered by a stimulus that normally would not elicit pain (allodynia) or would elicit only low-level pain (hyperalgesia), local numbness, burning sensations, or constant or intermittent spontaneous or provoked pain. NP can have a very significant impact of the patients' quality of life.

NP remains difficult to treat irrespective of its origin. It is refractory to standard analgesics, and recommended drugs, of middling efficacy, were not initially developed for this indication.

The market for Pharmaleads DENKIs

The world market for neuropathic pain management is estimated at €6 billion in 2015. This type of pain, mainly associated with diabetes, shingles, anti-tumoral and antiviral drugs, and surgery, affect 6 to 8% of the population in developed countries. This market is growing at a constant rate of 8 to 10% per annum.

Pharmaleads DENKIs, such as PL37, will constitute a true therapeutic progress in severe pain relief without the side effects of opiates and current treatments.

About Pharmaleads: www.pharmaleads.com

Founded in 2001 and based, in Paris, France, Pharmaleads has developed a coherent set of first-in-class molecules, thanks to its world-class medicinal chemistry expertise, providing ground-breaking solutions in pain treatment. Pharmaleads designs and manages the early-stage development of small protease inhibiting molecules for diagnostic and therapeutic use.

Articles on DENKIs recently published by Pharmaleads in major international journals:

Roques B.P., Fournié-Zaluski M.C., Wurm M. *Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain. Nature Rev. Drug Discov., 2012, 11, 292-310.*

Poras H., Bonnard E., Dangé E., Fournie-Zaluski M-C., Roques B.P. *New orally active dual enkephalinase inhibitors (DENKIs) for central and peripheral pain treatment. J. Med. Chem., 2014, 57, 5748-5763.*

Bonnard E., Poras H., Nadal X., Maldonado R., Fournie-Zaluski M-C., Roques B.P. *Long lasting oral analgesic effects of N-Protected aminophosphinic dual enkephalinase inhibitors (DENKIs) in peripherally-controlled pain. Pharma. Res. Per., 2015, 3(2), e00116, doi: 10.1002/prp2.116*

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