

# Xen2174

## A New Class of Pain Therapeutic

Safe, effective, well-tolerated therapeutics for the treatment of severe chronic pain are urgently needed. Current therapeutics are often inadequate, demonstrating variable efficacy and safety profiles and are frequently associated with unwanted side-effects. For this reason, there are currently more than 27 million people world wide receiving inadequate treatment for severe chronic pain. In particular, an estimated 75% of advanced cancer patients are not receiving suitable pain treatment. Furthermore, the number of people requiring effective pain treatment is expected to increase with the ageing population.

By focusing on the pathway that modulates severe pain signals, Xenome is developing Xen2174 as an effective and highly specific therapeutic aimed at the disruption of pain signals. With the potential for a combined safety and efficacy profile beyond that of currently available and emerging treatments, Xen2174 is poised to become a first-line therapeutic with applications in a broad range of severe pain types.

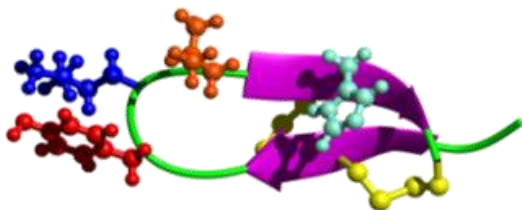
## Technology

Fig A:  
Diagram of  
Xen2174 based  
on NMR  
structure.

Fig B:  
Non-  
competitive  
inhibition of  
<sup>3</sup>H-NE uptake  
by Xen2174 at  
NET.

The norepinephrine transporter (NET) is a validated target for the development of pain therapeutics. NET is located on nerve endings that release norepinephrine (NE) into the synapse following nerve stimulation, and functions to regulate NE levels in the Central Nervous System (CNS). Xen2174 acts by selectively binding to NET, blocking its ability to remove NE from the synapse. As a result, NE levels in the spinal cord increase, leading to the suppression of pain messages.

Fig A:



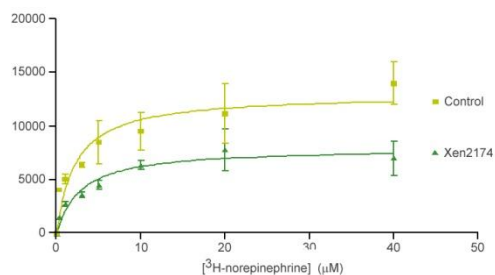
Xen2174 is a small (1400 Da), stable, highly structured peptide. It is derived from cone snail venom, and was further improved through a structure-activity program aimed at the optimization of potency, selectivity, efficacy, safety, stability and manufacture. The result is a new chemical entity representing a unique class of inhibitors with novel chemistry and pharmacology.

**Peptide Advantage:** To date, NET inhibitors have been small molecules and are frequently associated with either low efficacy or unwanted side effects. However Xen2174 is a stable peptide with the ability to non-competitively inhibit NET via allosteric modulation. This is anticipated to yield distinct clinical advantages, including a low side effect profile and an inability to overdose.

**Route of Administration:** Xen2174 is administered directly to the site of action via intrathecal (IT) delivery. Moreover, Xen2174 provides great potential to grow the underserved IT pain market with a safe and effective product.

**Ease of Manufacture:** Xen2174 is easily synthesized. Efficient, cost-effective, high-yield peptide manufacture and purification procedures have been established.

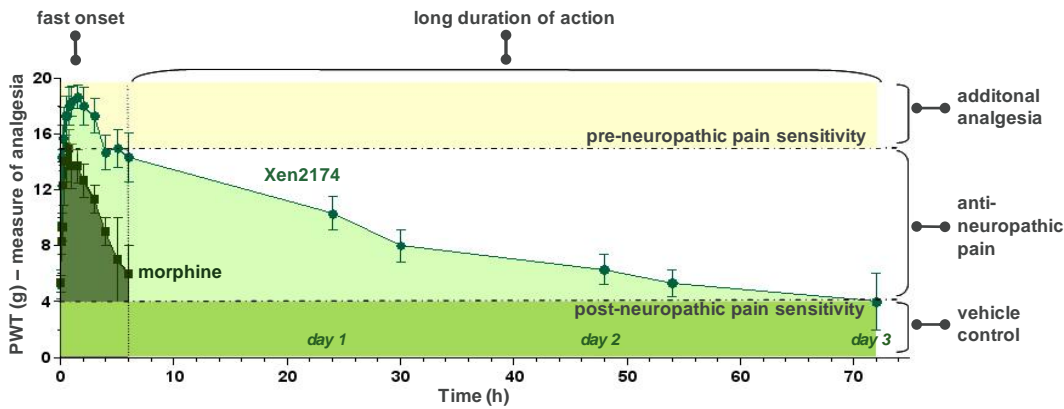
Fig B:



**Intellectual Property:** Xen2174 is protected by a comprehensive intellectual property portfolio of five families of granted patents and pending patent applications covering the broad class and lead compound, and its use in the treatment of pain.



Fig C:



**Fig C:** Xen2174 vs morphine: Xen2174 was compared to morphine in a neuropathic pain rat model. Xen2174 shows fast onset and demonstrates an extended duration beyond that of morphine. Xen2174 does not demonstrate a pain relief ceiling effect such as that seen with morphine.

## Data

### Pre-Clinical

Pre-clinical results for Xen2174 indicate excellent efficacy and tolerability in animal models.

- Highly efficacious in the treatment of acute post operative pain and chronic neuropathic pain
- Produces long lasting relief
- Well tolerated in animal models
- Synergistic with morphine
- More effective than morphine

### Clinical

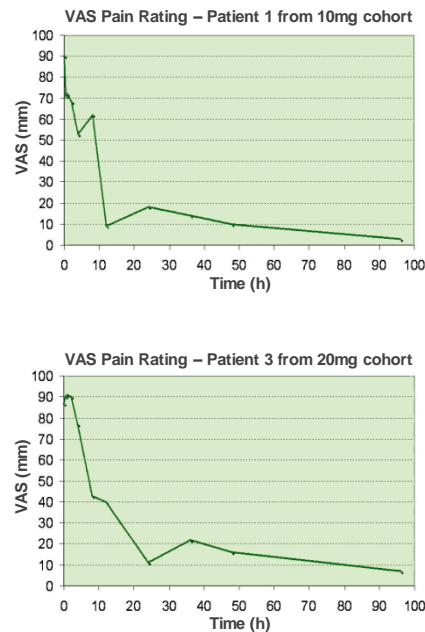
Xen2174 is now in a clinical trial program to assess its safety and efficacy in the treatment of both moderate to severe chronic and severe pain conditions.

**Phase I:** A double-blind, randomized, single I/V dose escalation study on healthy volunteers demonstrated that Xen2174 was safe and well-tolerated.

**Phase III – Severe Chronic Pain:** An open label, single IT bolus, dose-escalating study on cancer patients suffering severe chronic pain has been completed. Xen2174 was found to be well tolerated with a very acceptable side-effect profile across a wide range of dose levels. The study provided evidence that a single dose of Xen2174 can relieve pain quickly and for a sustained period (Fig D). These results provide a solid foundation for continued development.

**Phase II – Severe Acute Pain:** A randomized, placebo-controlled, single intrathecal injection study for acute post-operative pain using the bunionectomy model is currently underway. The study aims to assess the efficacy, safety, tolerability, dose-response, and duration of Xen2174 in an acute, post-surgical pain setting.

Fig D:



**Fig D:** Xen2174 Phase I/II results: Self - assessment of VAS pain score shown for two patients (one each from 10 mg and 20 mg cohorts). Evidence of efficacy is seen at all dose levels above 0.025 mg. At least one patient per cohort experienced >90% primary pain relief during the assessment period. Group mean pain scores showed a reduction in primary pain for the entire assessment period.

## About Xenome

Xenome is a discovery-based, biopharmaceutical company committed to the development of peptide drugs. Xenome's discovery and development activities are underpinned by its libraries of novel venom-derived peptides and peptidomimetics, its expertise in peptide chemistry and its understanding of the process for developing peptide drugs.

Xenome is interested in talking to companies eager to explore commercial partnerships for Xen2174 for both chronic and acute severe pain conditions.

For further information please contact:

Anthony Filippis, PhD MBA  
 Vice President, Business Development  
 Xenome Limited  
 ph: +61 7 3720 8055  
 mob: +61 419 507 880  
 anthony.filippis@xenome.com  
 www.xenome.com

