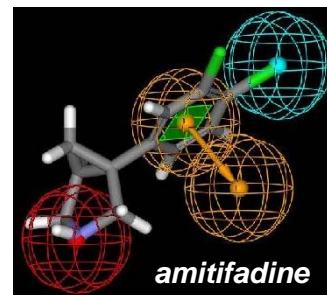


Ethismos Research

Ethismos has developed a breakthrough drug candidate, amitifadine, that prevents an irreversible acute to chronic neuropathic pain transition that affects 1 out of 2 patients in the months following breast cancer surgery (BCS). Chronic pain can lead to a lifetime struggle with pain management, costing the healthcare system millions of dollars per patient. Amitifadine, a triple reuptake inhibitor, modulates the brain's physiological reactions to pain by targeting the brain serotonin (5-HT), norepinephrine (NE) and dopamine (DA) pathways to prevent the acute to chronic pain transition.



Amitifadine is a safe, cost effective, nonaddictive, breakthrough preventative treatment poised to dramatically change the chronic pain management paradigm. Ethismos' goal is to complete Phase IIb clinical trials and compile the data necessary for acquisition or licensing by a strategic partner in the pain management arena.

Chronic Pain Market Landscape

Treating chronic pain is a lifelong challenge – there are few medications approved for chronic use, and many carry severe side effects. In addition, chronic pain can lead to other issues, such as opioid addiction and depression. There are estimates that the medications used to treat chronic pain can cost insurance companies approximately \$1 trillion a year. About 92% of women diagnosed at Stage I/II begin their journey with BCS. Unfortunately, in spite of excellent cancer survival outcomes, unremitting chronic pain and sensory disturbances as a result of the surgery are all too common. Furthermore, there are known risk factors that increase the likelihood of developing chronic pain, such as anxiety, depression, acute pain and pain catastrophizing. Using its drug candidate amitifadine, Ethismos is focused on preventing the onset of chronic pain, as opposed to treating it for life once it has manifested.

Amitifadine treats high risk symptoms of pre-op pain during the 2-weeks before surgery. Continuing treatment 12-weeks post-op reduces pain and emotional symptoms of pain that trigger the acute to chronic pain transition. Ethismos is focused on preventing chronic pain, as opposed to treating it for life.

The Pivot to Chronic Pain Prevention

Anthony McKinney, Founder and CEO of Ethismos, is a well-known drug developer and life science entrepreneur who has been involved in the development and exits of several successful companies and drug products. Anthony has been involved with the development of amitifadine for over a decade across multiple companies and multiple related indications in a long-term collaboration with the Chief of Psychiatry at Mass General Brigham, Dr. Maurizio Fava who has long been a champion for this multi-modal agent.



Anthony McKinney

The Fava collaboration eventually led to an introduction to one of the leading pain experts in the US, Dr. Robert Dworkin of University of Rochester, who is now a company director. Later, Dr. Dworkin introduced the Company to Professor Henrik Kehlet of Rigshospitalet, Copenhagen, a leader in the Prevention of Chronic Pain field who believed the amitifadine multi-modal pharmacology had the potential to be a game changer by suppressing pre-op symptoms that

place the patient at risk for long-term pain and by modulating DA during the 12-weeks post-surgery to block the emotional triggers of pain chronification.

The group postulated that amitifadine could leapfrog the current pain market leader, Cymbalta, commonly used to treat both mood disorders and pain. Cymbalta is a double reuptake inhibitor, affecting only Serotonin and Norepinephrine. Amitifadine brings the third leg of the prevention stool, Dopamine, into the equation. Previously, that was not possible because a rapid response in the Dopamine pathway caused negative side effects. Remarkably, amitifadine has clinically proven only a modulating effect on Dopamine, thus changing the game. As a triple reuptake inhibitor targeting Serotonin, Norepinephrine and Dopamine, Ethismos firmly believes that prescribing amitifadine for two weeks pre-op, to 'cool' the patient, followed by an additional 12 weeks post-op to prevent the transition from acute to chronic pain, the drug will remove the need for a lifetime of pain management.

Amitifadine, the Goldilocks Solution

Traditionally, the main problem of triple reuptake inhibitor drugs is that although effective, they have intolerable side effects. Even the most minimal effective doses are too severe for patients to tolerate. Amitifadine brings the perfect balance – as a reuptake inhibitor, it is just strong enough to be an effective drug without inducing serious side effects. Achieving this delicate balance makes this molecule the perfect solution to disrupt the pain management marketplace. Both amitifadine and its sister drug (acquired from Anthony McKinney by Otsuka and now past Phase III clinical trials) have ample clinical data proving that they are well tolerated by patients.

	Amitifadine	Traditional Chronic Pain Treatment (opioids)	Traditional Chronic Pain Treatment (Cymbalta)
Preventative vs. Treatment	Preventative	Treatment	Treatment
Therapeutic Cycle	14-week	Intermittent, Lifelong	Intermittent, Lifelong
Safety	+++	---	++
Cost	+	+++	+
Dollar Sales	n/a	WW: \$25B; US: \$14B*	\$1.8B (36% of \$5B)***

***IQVIA peak sales

How Amitifadine will Change the Landscape

Ethismos is currently focused on completing Phase IIb trials of amitifadine to prove efficacy in women undergoing breast cancer surgery that present with one of the pre-op risk factors that increase likelihood of post-op chronic pain. Additionally, the company has plans to initiate a trial in patients undergoing total knee replacement surgery as a next indication. The ultimate goal is to get a designation from the FDA to treat all post-surgical chronic pain, for which clinical data with both soft tissue and orthopedic surgery are necessary. Ultimately, the goal is to present payors with the data that a 14-week course of amitifadine (with a cost of ~\$7 a day) will prevent chronic pain from developing after surgery, and thus should be prescribed for the 50 million surgical procedures a year, where chronic pain can develop. This will save the payors from the costs associated with the lifelong treatment of chronic pain and will shift the paradigm of chronic pain management from treatment to prevention.