Anesthetic HTX-011 Reduces Need for Opioids in Phase 3 Studies

CECILIA PESSOA GINGERICH

Recently published results from 2 randomized, placebo- and active-controlled, double-blind, phase 3 clinical studies show that the experimental drug HTX-011 reduces pain intensity and the need for opioid rescue medication in post-operative patients.

The studies included patients undergoing bunionectomy (EPOCH1) and hernia repair (EPOCH2). HTX-011 achieved all primary and secondary endpoints in both studies, resulting in significant reductions in pain intensity and opioid medication use in the 72 hours after the surgery.

Specifically, the primary endpoint was pain intensity as measured by the Area Under the Curve (AUC) score from 0 to 72 hours post-surgery (AUC 0-72) compared to placebo. Key secondary goals included comparison of pain intensity by AUC 0-72 to bupivacaine solution, the amount of opioid rescue medication consumed compared to placebo in the 72 hours after surgery.

FDA Announces New Approval of Daptomycin For Injection in Adult Patients

JENNA PAYESKO

Fresenius Kabi has announced that the US Food and Drug Administration (FDA) has approved the abbreviated new drug application of daptomycin for injection as an antibiotic and generic alternative to Cubicin.

Daptomycin for injection will be available as a single dose vial containing 500 mg lyophilized powder for reconstitution per vial, providing patients with an additional source of this antibiotic.

The lipopeptide antibacterial is indicated for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae subsp. equisimillis and Enterococcus faecalis in adult patients and Staphylococcus aureus bloodstream infections in adult patients, including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

“The approval provides Fresenius Kabi and its customers an additional source of this important antibiotic,” the statement said.
the proportion of patients who did not use opioids after surgery compared to bupivacaine solution, and total opioid consumption in the 72 hours following surgery compared to bupivacaine.

This week, President Trump announced a plan that included a call for a decrease in the use of opioid medication. The plan also called for research into and development of non-addictive pain management options as alternatives to opioid prescriptions.

There is a “desperate need for effective non-opioid alternatives,” said Eugene R. Viscusi, MD, Professor of Anesthesiology and Chief of Pain Medicine in the Department of Anesthesiology at the Sidney Kimmel Medical College of Thomas Jefferson University in Philadelphia in a statement. “The phase 3 results with HTX-011 suggest it may be a promising foundation in non-opioid multimodal pain management in a wide range of surgical procedures.”

Both studies did see significant differences in pain intensity when compared to placebo or bupivacaine treatment. There was a 23% reduction in pain intensity as measured by AUC 0-72 when comparing HTX-011 to placebo in the EPOCH2 study, and a 21% reduction when compared to the bupivacaine treatment. EPOCH1 saw a 27% reduction in pain intensity as measured by AUC 0-27 compared to placebo and 18% compared to the bupivacaine solution.

A previous study of thoracic surgery has shown that post-operative opioid prescriptions can place patients at risk of becoming addicted to these medications, contributing to the country’s opioid use epidemic.

“This fast-moving epidemic affects both men and women, and people of every age,” said CDC Acting Director Anne Schuchat, M.D. in a statement. “It does not respect state or county lines and is still increasing in every region in the United States.”

HTX-011 was designed to relieve patient pain while reducing the need for opioid medications which carry the risks of abuse and addiction. Both studies saw reductions in the amount of opioid medication patients consumed after surgery.

Following bunionectomy, patients receiving HTX-011 consumed 37% less opioid medication in the 72 hours following surgery than placebo patients and 25% less opioid medication than patients receiving the standard dose of bupivacaine solution. Furthermore, 29% of patients receiving HTX-011 required no opioid medication in the 72 hours post-surgery compared to only 2% receiving placebo and 11% receiving the standard-of-care, bupivacaine solution.

 Patients recovering from hernia repair surgery also consumed less medication than the other groups in the 72 hours after surgery (38% less than placebo, 25% less than bupivacaine). In this study, 51% of patients receiving HTX-011 required no opioid medication for 72 hours post-surgery compared to only 22% receiving placebo and 40% receiving the standard-of-care, bupivacaine solution.

HTX-011 was granted Fast Track Designation by the FDA in late 2017 and Heron Therapeutics, Inc. announced that it intends to submit the drug for FDA approval in the second half of 2018.

"ANESTHETIC HTX-011" CONTINUED FROM PAGE 1

Daptomycin is available immediately for those in the US and will be offered as a Novaplus private-label option for Vizient, Inc. members.

The most common adverse reactions in adult cSSSI patients for injection 4 mg/kg (≥2%) are diarrhea, headache, dizziness, rash abnormal liver function tests, elevated CPK, urinary tract infections, hypotension and dyspnea.

Common side-affects in adults with Staphylococcus aureus bacteremia/endocarditis receiving daptomycin for injection 6 mg/kg (≥5%) are sepsis, bacteremia, abdominal pain, chest pain, edema, pharyngolaryngeal pain, pruritic, increased sweating, insomnia, elevated creatinine phosphokinase and hypertension.

Daptomycin for injection is not indicated for treatment of pneumonia, left-sided infective endocarditis due to Staphylococcus aureus or recommended in pediatric patients younger than 1 year of age due to risk of potential effects on muscular, neuromuscular and/or nervous systems observed in neonatal dogs.

To maintain the effectiveness of Daptomycin for injection and other antibacterial drugs and reduce development of drug-resistant bacteria, the treatment should only be used for infections that are proven or strongly suspected to be caused by bacteria.

Fresenius Kabi also offers daptomycin for injection that’s produced by a third party under a separate, previously approved abbreviated new drug application.
Researchers Investigate Natural Pain Killing Circuit in the Brain

EMMA YASINSKI

When thinking of painkillers, more often than not, the mind settles on opioids—the drugs at the heart of a current overdose epidemic in the United States. But the body has its own, natural pain-killing mechanisms as well, and a recent study by researchers at the University of Cambridge and the Advanced Telecommunications Research Institute International in Japan has shed light on how this natural pain-killing circuit is activated in the brain.

The study authors hope that the information will help researchers understand what goes wrong in patients with chronic pain, and possibly lead to safer and more effective treatments. Scientists know very little about how we feel and reduce pain naturally, and the mechanisms of existing treatments are poorly understood.

“We recognize that persistent pain (e.g. after injury) is a valuable signal—it tells us to stop doing other things, and rest and

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Eptinezumab Reduces Migraines Over Long-Term PROMISE 1 Results

KEVIN KUNZMANN

New 12-month data from a phase 3 trial testing the efficacy of eptinezumab for the prevention of migraines has shown the calcitonin gene-related peptide (CGRP)-targeting therapy is capable of reducing migraines at 2 different doses.

The results from Alder Biopharmaceutical’s Prevention of Migraine via Intravenous Eptinezumab Safety and Efficacy 1 (PROMISE 1) clinical study demonstrated reductions in migraine following study third and fourth quarterly infusions of both 100 mg and 300 mg eptinezumab versus placebo in patients with episodic migraines. PROMISE 1 also reported a comparable safety profile to that of previous trials involving eptinezumab. The news bodes well for eptinezumab, as Alder hopes to have it approved by the US Food and Drug Administration (FDA) as the first migraine infusion therapy.

The original double-blind, placebo-controlled global trial randomized 888 qualified patients to receive either eptinezumab (300 mg, 100 mg, or 30 mg), or placebo infusion, once-weekly for 12 weeks. All patients had previously experienced at least 14 headache days per month, with 4 of such headaches meeting the criteria for migraine.

Primary endpoint for the trial was mean change from baseline in monthly migraine days over the treatment period. Results presented at the AAN meeting focused on the therapy’s extended results through month 12.

For the long-term analysis, patients were dosed once every 3 months. Through months 6-12, 70.7% of patients to receive eptinezumab reported an average reduction of
50% or greater of monthly migraine days from baseline, compared to just 58.7% for patients given placebo. The reduction was an 8.9% improvement from mean reductions reported during the first 2 quarterly doses of therapy.

Another 51.5% of eptinezumab patients reached a mean monthly migraine day reduction of 75% or greater from baseline. Just 38.7% of patients given placebo reported that rate. This reduction was 12.8% improvement on that reduction reported by patients given therapy in the first 2 quarterly doses.

From its safety profile, the most commonly reported adverse events in all eptinezumab treatment groups were upper respiratory infection (10.5%), nasopharyngitis (6.8%) and sinusitis (3.6%).

Stephen D. Silberstein, MD, professor of Neurology and director of the Jefferson Headache Center at Thomas Jefferson University, said in a statement that it is exciting to see such encouraging results in investigative migraine prevention therapy.

“I see a significant need for my patients for a treatment that provides rapid, effective, well-tolerated and long-term results and I’m looking forward to the FDA’s review of these data,” Silberstein.

Eptinezumab is also backed by another phase 3 trial (PROMISE 2), in which 1072 patients were randomized to receive either eptinezumab (300 mg or 100 mg) or placebo. In January, Alder reported that therapy again met its primary endpoint of mean change from baseline in monthly migraine days over the 12 week treatment period. It also met secondary endpoints of reduction in migraine prevalence day 1 and days 1-28; reduction in mean monthly migraine days of at least 50%, 75%, and 100% from baseline; change from baseline in mean monthly acute migraine-specific medication days; and reductions from baseline in patient-reported impact scores on the Headache Impact.

It takes us 1 step closer to being able to harness the brain’s natural pain relief system in a more specific way than just giving opioids,” he said. “Putting together the brain circuits is really crucial basic science that we need to get in place to make eventual progress on the clinical front.”

The study, “The control of tonic pain by active relief learning,” was published in eLife.
Major Cannabis Study Forthcoming in Philadelphia

JARED KALTWASSER

Researchers in Pennsylvania are preparing to launch a major study designed to detail the benefits of medical marijuana as an alternative to opioids for pain management.

Marijuana, referred to medically as cannabis, is increasingly available to patients, with 29 states legalizing the drug as a medical therapy. However, the medical literature on the use of marijuana for pain management is relatively thin.

Ari C. Greis, DO, a clinical assistant professor in the Department of Physical Medicine and Rehabilitation at the Rothman Institute, part of Thomas Jefferson University, will lead the study. He told MD Magazine this will be the first of several studies looking at cannabis as a pain management strategy.

“There are already several observational studies showing a relationship between cannabis use and reduced opioid intake,” Greis said. “But we clearly need more high-quality, prospective studies to assess the effects of specific cannabinoid preparations on common pain conditions.”

The first study will focus on patients with lower back and leg pain associated with compression of spinal nerves or sciatica.

Greis said he believes cannabis can be an important part of a multimodal approach to pain management. He said the evidence for marijuana as a pain management treatment is mounting, even as new research is calling into question the efficacy of opioids.

“Recent studies are showing that opioids don’t work well for chronic pain, and the available literature on cannabis for pain is very promising,” he said. “Having access to cannabis seems to reduce opioid use and related overdose mortality rates. We must find safer alternatives to opioids.”

If cannabis helps reduce the use of opioids, it would hopefully also reduce rates of dependence on opioids, Greis said.

The Rothman Institute is one of the country’s largest orthopedic practices. For funding, it will partner

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Minnesota Cannabis Patients Report Positive Pain Management Results

JARED KALTWASSER

A survey of medical cannabis users in Minnesota shows 4 in 10 feel the drug has given them significant pain reduction.

The data are based on self-evaluations by 2174 patients enrolled in the state’s medical cannabis program during the last 5 months of 2016. Those patients were required to complete a pain, enjoyment, general activity (PEG) assessment on a scale of 1 to 10 prior to each purchase.

Those self-reports showed 42% of patients had pain reductions of more than 30% or more. Nearly one-quarter of participants maintained the 30%-or-more pain-reduction threshold over the course of the study. Fifty-five patients reported severe adverse effects (sAEs).

Tom Arneson, MD, MPH, the research manager for the Minnesota Department of Health’s Office of Medical Cannabis, said the study is part of the state’s ongoing evaluation of its program. He said it is important not to overemphasize the results of the study since it comes with some significant limitations. The data is based mostly on self-assessment, with a small component based on physician surveys. The study also has no control group.

“However, I have spoken with several clinicians with patients enrolled in the program and they indicate the numerical data and patient statements included in the report generally matched their observations—that some patients appear to have benefitted very much and that many were able to reduce or get off their opioid medications,” Arneson told MD Magazine.

Of the 353 patients in the study who said they were taking opioids

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in the study with Ananda Hemp, a provider of health and wellness products derived from industrial hemp cultivated in Kentucky.

The study is being run out of Thomas Jefferson University’s Lambert Center for the Study of Medicinal Cannabis and Hemp. Greis said his colleagues are championing innovation and are eager to find better alternatives to opioids. However, Greis conceded that some physicians he speaks to at other clinics are still cautious about cannabis.

“But I also hear from many pain management physicians who fear prosecution from the Drug Enforcement Agency if they recommend cannabis or allow cannabis use while on opioids,” Greis said. “And that’s very unfortunate in my opinion.”

Greis said he does not believe marijuana deserves to be classified as a Schedule I drug, and he suspects most physicians agree with him. Greis said there is ample evidence to suggest that society should err on the side of increased access to marijuana, even as researchers continue to study the drug and its effects.

David L. Nathan, MD, DFAPA, the current president of the board of directors of Doctors for Cannabis Regulation, agrees. He told MD Magazine that “federal legalization will increase patient access, but perhaps more importantly it will help remove the stigma that continues to prevent patients—including many on high doses of potentially lethal opioids—to avail themselves of a potentially better tolerated medication.”

As of March 2, 2018, the State of Pennsylvania stated that 21,000 patients had applied to be part of the state’s medical marijuana program, with 6000 of those patients already approved by their physicians. Just over one-third of those patients—2200—had received medical marijuana through one of the state’s dispensaries as of March 2.

at the time of their enrollment in the medical cannabis program, 63% said they were able to reduce or eliminate opioid use within six months of using cannabis. The physician survey component of the study showed a similar amount (58%) of patients were able to reduce the use of other pain medications.

Arneson said the data should not be read as indicating that cannabis can be a replacement for opioids. However, he said the study does add important context to the ongoing re-evaluation of pain-management tactics currently taking place in clinics across the country due to the opioid addiction crisis.

“Our report adds to evidence that cannabis medications might have a role to play, but there is still too little known to have a clear sense of that role: for what patients, in what settings, what types of medical cannabis products, etc.,” he said.

Marcus Plescia, MD, MPH, the chief medical officer for the Association of State and Territorial Health Officials, said 29 states now have legislation enabling the use of cannabis for certain medical conditions. Of those, 8 have legalized marijuana for recreational use.

Plescia said the enactment of this legislation has put state health departments in a tricky position, since federal law still bans the use of marijuana, and thus the US Food and Drug Administration (FDA) has not approved the use of medical cannabis.

“We usually rely on the FDA to regulate medications, and this is a case where that regulation is not as strong as it would be with something where there are clear federal guidelines,” he said. “That’s probably the main concern we have.”

Plescia said another concern he has generally with marijuana legalization is that it might cause some people to assume marijuana has no harmful effects at all. He said there can be medical issues associated with marijuana dependence, and there’s also a question of what impact marijuana smoke can have on the lungs after long-term use.

That’s why Plescia said his organization wants to make sure states do a good job of tracking marijuana use and its effects.

“We want to make sure that as states pass these laws that they put in place robust surveillance systems,” he said. “That is a key point to us. We’ve got to monitor this and make sure have some way of looking at how this affects the general population.”

The results of Minnesota’s study, “Intractable Pain Patients in the Minnesota Medical Cannabis Program: Experience of Enrollees During the First Five Months,” are published online.
Failed Osteoarthritis Drug May Mitigate Neuropathic Pain and Reduce Dependence

EMMA YASINSKI

A drug that failed phase 2 studies for osteopathic pain may be granted new life as a way to treat neuropathic pain while leading to less tolerance and fewer withdrawal effects than opioids.

The drug, LY2828360, a cannabinoid type 2 (CB2) receptor agonist, was developed by Eli Lilly, and while it was not shown to decrease knee pain in osteopathic patients, it has already been deemed safe for use in humans.

“The fact that LY2828360 had already been shown to be safe in people was very exciting to us because if it was effective in blocking pain for a different, new indication (i.e. neuropathic pain due to chemotherapy treatment), it would mean that it would make the prospects of rapid translation to evaluation in the clinic possible,” Andrea Hohmann, PhD, ScM, BSc, a professor in the Indiana University Bloomington College of Arts and Sciences’ Department of Psychological and Brain Sciences, and lead author of the study, told MD Magazine.

First, the researchers used a chemotherapy drug, paclitaxel, to induce neuropathic pain in male mice. They tested these mice and confirmed that they had hypersensitive responses to cold and mechanical stimulation, implying that they had developed neuropathic pain from the drug. Next, they gave the mice morphine. As expected, these mice developed a tolerance to the drug, as well as a physical dependence. The researchers measured this physical dependence by observing the withdrawal symptoms after giving the mice naloxone, an opioid blocker.

The team used LY2828360 in 2 experimental groups—in the first, they gave a little bit of LY2828360 cont...
Erenumab was the first drug in its category when Novartis filed with the US Food and Drug Administration (FDA) last year. The FDA approved the Biologics License Application for treatment in patients who experience migraines 4 or more days each month.

“Migraine is a serious, chronic neurological disease with a profound and limiting impact on patients’ abilities to carry out everyday tasks,” said Vas Narasimhan, MD, who is currently CEO of Novartis.

The safety and tolerability profile of erenumab was comparable to placebo and no patients in the erenumab group discontinued due to adverse events.

“Our results show that people who thought their migraines were difficult to prevent may actually have hope of finding pain relief,” said Reuter. “More research is now needed to understand who is most likely to benefit from this new treatment.”

Additionally, the short, 3-month length of the study limited the results. Further study is needed to confirm whether benefits from erenumab continue on a long-term scale.

Failed Osteoarthritis

with each dose of morphine. In the second, they treated the mice for 2 weeks with LY2828360 first, and then switched to morphine. In both groups, the experimental drug seemed to prevent tolerance and reduce the signs of withdrawal. The higher dose of LY2828360 provided pain relief to the mice, even during the 2 weeks when they did not receive any morphine.

“Our studies suggest that the CB2 agonist was effective in treating established neuropathic pain in mice,” Hohmann said. “The target is very promising because activation of this receptor unlikely to be associated with psychoactivity, physical dependence or addiction.”

Along with testing the efficacy of the drug in humans with neuropathic pain, the team is also planning more studies to better understand the drug’s mechanism of action. They will use mice with the CB2 receptor knocked out in specific tissues, to understand how the drug exerts its effects, and whether or not it might be useful for other types of pain.

“Unlike CB1 receptors, which are found at high levels in the brain, CB2 receptors are mostly expressed in immune cells and are largely absent from the brain,” Hohmann said. “We still need to better understand the cell types that contain CB2 receptors that are responsible for both the analgesic effects of LY2828360 and the ability of this compound to reduce opioid tolerance and physical dependence.”

The study, “Slowly Signaling G Protein–Biased CB2 Cannabinoid Receptor Agonist LY2828360 Suppresses Neuropathic Pain with Sustained Efficacy and Attenuates Morphine Tolerance and Dependence,” was published in the Journal of Molecular Pharmacology.