Adolore BioTherapeutics Presents Promising Preclinical Data Supporting Its Innovative Gene Therapy to Treat Chronic Pain

Innovative rdHSV-based CA8 gene therapy demonstrates preclinical proof-of-concept as a disease-modifying long-acting local analgesic to replace opioids in chronic osteoarthritis (OA) knee pain management*

DELRAY BEACH, FL. – December 5, 2023 – Adolore BioTherapeutics ("Adolore" or the "Company"), a biotechnology company focused on developing breakthrough opioid-free gene therapy treatments for chronic pain, today announced the presentation of preclinical data for its innovative CA8* (*Carbonic Anhydrase-Like Analgesic Peptides, CA8 Variants) gene therapy, rdHSV-CA8* demonstrating the potential of Adolore's innovative first- and best-in-class, long-acting local analgesics that represent Disease-Modifying Anti-Pain therapies (DMAPs) with the capability to alter the underlying pathophysiology of chronic pain.

"We were honored to showcase some of the encouraging preclinical data we have gathered to date which supports our innovative approach to chronic pain treatment through our proprietary nontoxic JDNI8 replication-deficient (rd)HSV-based disease-free gene therapy vectors expressing long-term carbonic anhydrase-8 analgesic peptide variants (CA8*). There remains a significant and growing need to provide an alternative to the currently available and widely used opioid pain treatments that are systemic, short-acting and complicated by diversion, dependence, tolerance, abuse, addiction, and death," commented Dr. Levitt. "We continue to believe in this innovative approach to potentially address the significant unmet need for safe and effective non-opioid pain therapies to replace opioids and and our preclinical data strongly support continued development progressing toward the clinics."

Two presentations were made on rdHSV-CA8* preclinical data. The first presentation was entitled: *Replication-deficient Herpes Simplex Carbonic anhydrase 8 non-opioid analgesic gene therapy treats chronic osteoarthritis pain by activating sensory neuron Kv7 voltage-gated potassium channels.*

Preclinical data were presented from studies designed to test the hypothesis that novel JDNI8 replication-defective herpes simplex-1 viral vectors (rdHSV) expressing a carbonic anhydrase-8 analgesic peptide variant would treat monoiodoacetate-induced (MIA) chronic OA knee pain using the intra-articular knee joint (KJ) route of administration.

Key Highlights:

- rdHSV-CA8* KJ injections inhibited MIA-induced chronic OA mechanical pain by Day 6, returned to Baseline mechanical thresholds by Day 13, and exceeded Baseline (analgesia/anti-nociception) by Day 20 and persisted out to Day 56 as compared to negative controls, which never exceeded Baseline mechanical thresholds.
- rdHSV-CA8* also improved voluntary wheel running, weight-bearing and rotarod function.
- Using allometric conversion, this rdHSV-CA8*-induced analgesia/antinociception was estimated to be equivalent to >100 mg of oral morphine in an average-sized adult dosed routinely each day for over 56 days.
- Kv7 channel specific inhibitor XE-991 reversed rdHSV-CA8*-induced anti-hyperalgesia and analgesia in a dose- and time-dependent manner confirming selective activation of Kv7 voltage-gated potassium channels is involved in these rdHSV-CA8* therapeutic effects.
- These data demonstrate for the first time local KJ administration of rdHSV-CA8* produces Kv7 channel activation to generate profound prolonged analgesia in this MIA-induced chronic OA pain model.

A second presentation was made entitled: *Replication-defective HSV carbonic anhydrase-8 non-opioid analgesic prolongs afterhyperpolarization in small rat primary afferents via activation of Kv7 channels.*

Using rdHSV-CA8* researchers were able to show robust transduction of primary afferent sensory neurons in vitro. Whole-cell current-clamp recordings were obtained 48 hours after infection with rdHSV-CA8* or negative control virus of these dissociated small (<30 µm) ganglion sensory neurons, selected by green fluorescence. Neurons were depolarized by brief square current command pulses.

Key Highlights:

- There were no changes in resting membrane potential, amplitude or duration of the action potential between rdHSV-CA8* or negative control infected neurons. rdHSV-CA8* as compared to negative controls significantly prolonged the afterhyperpolarization (AHP) duration (419±187ms vs 232±148 ms, P=0.006) and enhanced AHP peak amplitude (-9.3±4.9 mV vs -6.2±3.4 mV, P=0.003).
- These changes in AHP by rdHSV-CA8* but not negative controls were completely reversed by the selective Kv7 blocker, XE-991. Other K+ channel

blockers (eg, apamin, iberiotoxin, glibenclamide) failed to reduce AHP in rdHSV-CA8* infected neurons.
- These results were consistent with vHCA8 attenuating neuronal excitability via activation of Kv7 voltage-gated potassium channels known to be important analgesic therapeutic targets.

There are currently very few safe, efficacious non-opioid analgesic treatments for chronic pain sufferers on the market creating a very urgent unmet need. Leveraging its innovative CA8* gene therapy, the Company is currently advancing two preclinical development programs, ADB-101 for the treatment of patients' chronic pain caused by erythromelalgia, an orphan disease, and ADB-102 for the treatment of patients with chronic pain caused by knee OA. Based on compelling data generated to date, the Company is progressing these programs towards an IND filing and first in human clinical studies.

About Carbonic Anhydrase-8 (CA8*) Gene Therapy

CA8* (*Carbonic Anhydrase-Like Analgesic Peptides, CA8 Variants) gene therapies are a novel class of Kv7 activators that are long-acting and locally administered with proven analgesic efficacy. They provide for versatile dosing regimens and routes of administration, including intra-articular, intra-neuronal (nerve block) and intradermal injection. This non-opioid CA8* mechanism-of-action addresses neuropathic, inflammatory, and nociceptive pain, which apply to a broad range of chronic pain indications, including osteoarthritis pain, diabetic neuropathy, post-herpetic neuralgia, lower back pain, and cancer pain, as well as rare pain conditions such as erythromelalgia, an orphan drug disease. Using a replication-defective HSV vector enables disease-free localized delivery to the peripheral somatosensory nervous system with an excellent safety profile. HSV vectors are known for their stability and prolonged gene-expression, providing an excellent basis for long-term treatment.

About Adolore BioTherapeutics, Inc.

Adolore BioTherapeutics, Inc., is a biotechnology company focused on developing novel therapies for the treatment of chronic pain and other pain and nervous system conditions or disorders. Our best-in-class programs are long-acting, locally acting gene-therapies that are opioid-free Disease Modifying Anti-Pain therapies (DMAPs) for the treatment of chronic pain.

The Company's two current CA8* gene therapy programs are in preclinical development for treatment of patients suffering from erythromelalgia, a life-long heritable chronic pain condition representing an orphan drug disease with no approved therapy, and chronic osteoarthritis knee pain, affecting a large number of patients that is often treated with opioids due to the lack of good alternatives, thus contributing to the ongoing opioid crisis.

For more information, visit adolore.com.

Forward Looking Statements

To the extent this announcement contains information and statements that are not historical, they are considered forward-looking statements within the meaning of the federal securities laws. You can identify forward-looking statements by the use of the words "believe," "expect," "anticipate," "intend," "estimate," "project," "will," "should," "may," "plan," "intend," "assume" and other expressions which predict or indicate future events and trends and which do not relate to historical matters. You should not rely on forward-looking statements, because they involve known and unknown risks, uncertainties and other factors, some of which are beyond the control of the Company. These risks and uncertainties include, but are not limited to, those associated with drug development. These risks, uncertainties and other factors may cause the actual results, performance or achievements of the Company to be materially different from the anticipated future results, performance or achievements expressed or implied by the forward-looking statements.

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