# Zevra Announces Publication of MIPLYFFA® Mechanism of Action Manuscript in Molecular Genetics and Metabolism

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CELEBRATION, Fla., April 17, 2025 (GLOBE NEWSWIRE) -- Zevra Therapeutics, Inc. (NasdaqGS: ZVRA) (Zevra, or the Company), a commercial-stage company focused on providing therapies for people living with rare disease, today announces the publication of “Mechanistic insights into arimoclomol mediated effects on lysosomal function in Niemann-pick type C disease” in *Molecular Genetics and Metabolism.*

“This elucidation of MIPLYFFA’s ® highly differentiated mechanism of action marks a critical step in understanding its interactions with Niemann-Pick disease type C (NPC) at a cellular level,” said **Adrian Quartel, MD, FFPM, Zevra’s Chief Medical Officer. “**These insights further confirm that MIPLYFFA addresses the underlying pathology of NPC and supports the long-term treatment benefit observed in our clinical trials. Our findings may inform more effective treatment strategies for patients.”

The publication presents data demonstrating that arimoclomol enters the cell and increases the translocation of translation factors EB and E3 (FTEB & TFE3) from the cytosol to the nucleus, a key initial step for triggering a cascade of downstream events. Specifically, TFEB & TFE3 upregulate the coordinated lysosomal expression and regulation (CLEAR) genes including NPC1, which is essential for the regulation of lysosomal function. Increased CLEAR gene expression then causes higher NPC1 protein levels in the lysosomes, leading to greater correction of aberrant cholesterol trafficking. Of note, in animal NPC models, greater correction of aberrant cholesterol trafficking was shown to correlate with the improvement of specific neurological behaviors, such as rearing and gait.

**About MIPLYFFA® (arimoclomol)**

MIPLYFFA (arimoclomol) is Zevra’s approved therapy for use in combination with miglustat for the treatment of Niemann-Pick disease type C (NPC). Approved by the U.S. Food and Drug Administration on Sep. 20, 2024, MIPLYFFA (arimoclomol) increases the activation of the transcription factors EB (TFEB) and E3 (TFE3) resulting in the upregulation of coordinated lysosomal expression and regulation (CLEAR) genes. MIPLYFFA has also been shown to reduce unesterified cholesterol in the lysosomes of human NPC fibroblasts. The clinical significance of these findings is not fully understood. In the pivotal phase 3 trial, MIPLYFFA halted disease progression compared to placebo over the one-year duration of the trial when measured by the only validated disease progression measurement tool, the NPC Clinical Severity Scale. MIPLYFFA has also received Orphan Medicinal Product designation by the European Medicines Agency (EMA) for the treatment of NPC.

**INDICATIONS AND USAGE**

MIPLYFFA is indicated for use in combination with miglustat for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older.

**IMPORTANT SAFETY INFORMATION**

**Hypersensitivity Reactions:**
Hypersensitivity reactions such as urticaria and angioedema have been reported in patients treated with MIPLYFFA during Trial 1: two patients reported both urticaria and angioedema (6%) and one patient (3%) experienced urticaria alone within the first two months of treatment. Discontinue MIPLYFFA in patients who develop severe hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, stop MIPLYFFA and treat promptly. Monitor the patient until signs and symptoms resolve.

**Embryofetal Toxicity:**
MIPLYFFA may cause embryofetal harm when administered during pregnancy based on findings from animal reproduction studies. Advise pregnant females of the potential risk to the fetus and consider pregnancy planning and prevention for females of reproductive potential.

**Increased Creatinine without Affecting Glomerular Function:**
Across clinical trials of MIPLYFFA, mean increases in serum creatinine of 10% to 20% compared to baseline were reported. These increases occurred mostly in the first month of MIPLYFFA treatment and were not associated with changes in glomerular function.

During MIPLYFFA treatment, use alternative measures that are not based on creatinine to assess renal function. Increases in creatinine reversed upon MIPLYFFA discontinuation.

**The most common adverse reactions** in Trial 1 (≥15%) in MIPLYFFA-treated patients who also received miglustat were upper

respiratory tract infection, diarrhea, and decreased weight.

Three (6%) of the MIPLYFFA-treated patients had the following adverse reactions that led to withdrawal from Trial 1: increased serum creatinine (one patient), and progressive urticaria and angioedema (two patients). Serious adverse reactions reported in MIPLYFFA-treated patients were hypersensitivity reactions including urticaria and angioedema.

**Call your doctor for medical advice about side effects. You may report side effects to Zevra at 1-844-600-2237, or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**Drug Interaction(s):**
Arimoclomol is an inhibitor of the organic cationic transporter 2 (OCT2) transporter and may increase the exposure of drugs that are OCT2 substrates. When MIPLYFFA is used concomitantly with OCT2 substrates, monitor for adverse reactions and reduce the dosage of the OCT2 substrate.

**Use in Females and Males of Reproductive Potential:**
Based on animal findings, MIPLYFFA may impair fertility and may increase post-implantation loss and reduce maternal, placental, and fetal weights.

**Renal Impairment:**
The recommended dosage of MIPLYFFA, in combination with miglustat, in patients with an eGFR ≥15 mL/minute to <50 mL/minute is lower than the recommended dosage (less frequent dosing) in patients with normal renal function.

MIPLYFFA capsules for oral use are available in the following strengths: 47 mg, 62 mg, 93 mg, and 124 mg.

**About Zevra Therapeutics, Inc.**

Zevra Therapeutics, Inc. is a commercial-stage rare disease company combining science, data, and patient need to create transformational therapies for diseases with limited or no treatment options. Our mission is to bring life-changing therapeutics to people living with rare diseases. With unique, data-driven development and commercialization strategies, the Company is overcoming complex drug development challenges to make new therapies available to the rare disease community.

Expanded access programs are made available by Zevra Therapeutics, Inc. and its affiliates and are subject to the Company's Expanded Access Program (EAP) policy, as published on its website. Participation in these programs is subject to the laws and regulations of each jurisdiction under which each respective program is operated. Eligibility for participation in any such program is at the treating physician's discretion.

For more information, please visit www.zevra.com or follow us on X and LinkedIn.

**Cautionary Note Concerning Forward-Looking Statements**

This press release may contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include all statements that do not relate solely to historical or current facts, including without limitation statements regarding the sale of the PRV and anticipated proceeds therefrom; promise and potential impact of our preclinical or clinical trial data; the initiation, timing and results of any clinical trials or readouts, the content, information used for, timing or results of any NDA submissions or resubmissions for any products or product candidates for any specific disease indication or at any dosage; the potential benefits of any of our products or product candidates for any specific disease or at any dosage; future research and development activities; our strategic and product development objectives, including with respect to becoming a leading, commercially focused rare disease company; the potential benefits of our debt facility; our financial position, including our cash balance and anticipated cash runway; potential revenues from MIPLYFFA sales; potential revenues from our arimoclomol expanded access program in France; the potential for royalty and milestone contributions, the presentation of data at conferences; and the timing of any of the foregoing. Forward-looking statements are based on information currently available to Zevra and its current plans or expectations. They are subject to several known and unknown uncertainties, risks, and other important factors that may cause our actual results, performance, or achievements to be materially different from any future results, performance, or achievements expressed or implied by the forward-looking statements, including that the PRV sale is subject to conditions and may not close in the timeframe expected or at all. These and other important factors are described in detail in the “Risk Factors” section of Zevra’s Annual Report on Form 10-K for the year ended December 31, 2024, and Zevra’s other filings with the Securities and Exchange Commission. While we may elect to update such forward-looking statements at some point in the future, except as required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. Although we believe the expectations reflected in such forward-looking statements are reasonable, we cannot assure that such expectations will prove correct. These forward-looking statements should not be relied upon as representing our views as of any date after the date of this press release.

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