



New Publication Highlights Unique Properties of ATI-2138, a Potent and Selective Inhibitor of ITK and JAK3

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- Data Generated to Date Support Potential for Aclaris' ATI-2138 to Impact Several Human Inflammatory Diseases -

WAYNE, Pa., Feb. 12, 2025 (GLOBE NEWSWIRE) -- Aclaris Therapeutics, Inc. (NASDAQ: ACRS), a clinical-stage biopharmaceutical company focused on developing novel product candidates for immuno-inflammatory diseases, today announced the availability of a new publication describing the unique properties of Aclaris Therapeutics' ATI-2138, a novel investigational covalent inhibitor of interleukin-2-inducible T cell kinase (ITK) and Janus kinase 3 (JAK3) in development for the treatment of autoimmune and inflammatory diseases. This was published in *The Journal of Pharmacology and Experimental Therapeutics* and can be found [here](#).

"This publication provides important clinical and non-clinical evidence of the potential for ATI-2138 to be a best-in-class inhibitor of key signal transduction kinases as a result of its unique mechanism of action," said Dr. Joseph Monahan, Ph.D., Aclaris' Chief Scientific Officer. "ATI-2138 potently and selectively blocks both ITK and JAK3. Through this mechanism, ATI-2138 has been shown in preclinical studies to effectively inhibit Th1, Th2 and Th17 cell activity, which are key T cells involved in a wide range of autoimmune, chronic inflammatory and allergic diseases, including atopic dermatitis (AD), alopecia areata, and vitiligo. In addition, JAK inhibitors have been approved in multiple diseases including AD. Data generated to date support our ongoing clinical efforts including our ongoing Phase 2a trial of ATI-2138 in AD."

ITK regulates T cell receptor signal transduction and inhibition of this kinase can affect T cell differentiation and activation. JAK3 is a key signal transduction kinase that forms a heterodimer with JAK1, modulates JAK1 phosphorylation of signal transducer and activator of transcription 5 (STAT5), and regulates cytokines that signal through the IL-2 receptor common gamma chain (IL-2R γ) to affect lymphocyte proliferation and activation (Leonard and O'Shea, 1998; Rochman *et al.*, 2009; Agashe *et al.*, 2022).

The publication, entitled "*Characterization of the dual ITK/JAK3 small molecule covalent inhibitor ATI-2138*," describes in vitro and in vivo assessments and the clinical translation of ATI-2138 on ITK and JAK3 signaling. It describes the evaluation of the efficacy of ATI-2138 in three animal models of inflammatory disease, as well as the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) results of ATI-2138 in healthy human participants from single ascending dose (SAD) and multiple ascending dose (MAD) studies. The results in the publication include:

- **Biochemical Target Inhibition:** ATI-2138 covalently inhibits ITK, a TCR-activated Tec family kinase, more potently than the other Tec kinase family members and is selective for JAK3 inhibition relative to the other JAK isoforms.
- **Potency and Selectivity in Cellular Systems:** ATI-2138 dose-dependently decreased JAK1/JAK3-dependent IL-2-stimulated STAT5 phosphorylation in human peripheral blood mononuclear cells (PBMCs) with low-nanomolar potency while having no inhibitory effect on the JAK1/JAK2-dependent IFN γ -induced STAT1 phosphorylation or the JAK2/Tyk2-dependent IL-12-induced STAT4 phosphorylation, consistent with JAK3 selectivity.
- **Unique Pharmacological Profile:** In biochemical and cellular assays, ATI-2138 demonstrated a similar high potency for inhibiting both ITK and JAK3, compared to ritlecitinib which was markedly less potent in inhibiting T-cell receptor (TCR)-mediated ITK signaling.
- **Demonstrated Efficacy in Animal Models:** The functional cellular data demonstrating the impact of ATI-2138 on ITK and JAK3 biology translated into efficacy in multiple rodent models of chronic inflammation.
- **Well Tolerated in Initial Clinical Trials:** In healthy human participants, ATI-2138 was generally well tolerated at all doses tested in both the SAD and MAD trials. There were no clinically significant findings for laboratory results, vital signs, and ECGs. No participants experienced a serious adverse event (AE), serious AE related to the study drug, or an AE leading to death.
- **Activity on Target Biomarkers:** ATI-2138 demonstrated dose- and time-dependent modulation of biomarkers linked to both ITK and JAK3 activity in healthy human participants.

ATI-2138 is a novel pharmacologic agent that acts as a dual inhibitor of ITK and JAK3. The efficacy exhibited in preclinical animal models of inflammation and autoimmune diseases, coupled with the favorable safety, PK, and PD profile in healthy human SAD and MAD studies, support the potential for ATI-2138 to affect several human inflammatory diseases and further investigation of this molecule in patients with atopic and autoimmune diseases that are dependent on T cell function and/or IL-2R γ signaling.

About Aclaris Therapeutics, Inc.

Aclaris Therapeutics, Inc. is a clinical-stage biopharmaceutical company developing a pipeline of novel product candidates to address the needs of patients with immuno-inflammatory diseases who lack satisfactory treatment options. The company has a multi-stage portfolio of product candidates powered by a robust R&D engine. For additional information, please visit www.aclaristx.com.

Cautionary Note Regarding Forward-Looking Statements

Any statements contained in this press release that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “anticipate,” “believe,” “expect,” “intend,” “may,” “plan,” “potential,” “will,” and similar expressions, and are based on Aclaris’ current beliefs and expectations. These forward-looking statements include expectations regarding its development plans for ATI-2138, the potential for ATI-2138 to be a best-in-class inhibitor of key signal transduction kinases and the therapeutic potential of ATI-2138. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements. Risks and uncertainties that may cause actual results to differ materially include uncertainties inherent in the conduct of clinical trials, Aclaris’ reliance on third parties over which it may not always have full control, Aclaris’ ability to enter into strategic partnerships on commercially reasonable terms, the uncertainty regarding the macroeconomic environment and other risks and uncertainties that are described in the Risk Factors section of Aclaris’ Annual Report on Form 10-K for the year ended December 31, 2023, and other filings Aclaris makes with the U.S. Securities and Exchange Commission from time to time. These documents are available under the “SEC Filings” page of the “Investors” section of Aclaris’ website at www.aclaristx.com. Any forward-looking statements speak only as of the date of this press release and are based on information available to Aclaris as of the date of this release, and Aclaris assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise.

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