New Preclinical Data Further Support Potential for Tvardi's STAT3 Inhibitors in Ulcerative Colitis (UC)

September 24, 2026 12:00 PM EDT

In a preclinical chronic colitis model, Tvardi's oral small molecule accumulated in the colon at approximately 8-fold higher concentrations than in plasma, at pharmacologically relevant levels, and modulated STAT3-driven disease biology

Collective findings now span multiple preclinical models of UC, further supporting the scientific rationale for advancing TTI-109, Tvardi's next-generation STAT3 inhibitor, in UC

HOUSTON, Sept. 24, 2026 (GLOBE NEWSWIRE) -- Tvardi Therapeutics, Inc. ("Tvardi" or the "Company") (NASDAQ: TVRD), a clinical-stage biopharmaceutical company focused on the development of novel, oral small molecule therapies targeting STAT3 to treat inflammatory and proliferative diseases, today announced the publication of preclinical data evaluating Tvardi's STAT3 inhibitor in the *International Journal of Molecular Sciences*. The publication provides additional evidence supporting further investigation of STAT3 inhibition as a potential therapeutic approach to treating inflammatory bowel diseases, including ulcerative colitis (UC).

The publication, titled "Colitis-Associated Colorectal Cancer—STAT3 Inhibition as a Preventive Strategy," evaluated Tvardi's first-generation oral STAT3 inhibitor, TTI-101, in an azoxymethane (AOM)-dextran sodium sulfate (DSS) mouse model, designed to replicate the human progression from chronic colitis to colorectal cancer (CRC). Patients with UC are estimated to have a 20- to 30-fold higher risk of CRC than the general population. In this model, the orally administered STAT3 inhibitor reached pharmacologically relevant concentrations in the colon, normalized STAT3-regulated colonic gene expression and modulated proliferative programs associated with colitis-driven disease progression, preventing the development of colon polyps and adenocarcinomas. The chronic AOM-DSS prevention model is the fourth preclinical model of colitis in which Tvardi's STAT3 inhibitors have shown biological activity. Previously, Tvardi's oral small molecules normalized the UC hallmarks of immune dysregulation, inflammation and proliferation across three acute models representing distinct immune axes: DSS (innate/Th17), trinitrobenzene sulfonic acid (TNBS; adaptive Th1) and oxazolone (OXA; adaptive Th2/NKT).

"UC is a multifactorial disease shaped by three interconnected processes: immune dysregulation, inflammation and proliferation, each of which is regulated by STAT3. Current advanced therapies are designed primarily to target inflammation," said Imran Alibhai, Ph.D., Chief Executive Officer of Tvardi Therapeutics. "Even patients who reach endoscopic remission are not disease-free: 98% retain lesions composed of B- and T-cell aggregates, inflammatory infiltrates and distorted crypts associated with the chronic disease characteristics of UC. In this preclinical model, oral STAT3 inhibition achieved high exposure in the colon and normalized gene expression spanning unique STAT3-regulated programs associated with relapse and progression. We believe these findings demonstrate the potential of STAT3 inhibition in modulating multiple aspects of the underlying disease biology with a profile favorable for gastrointestinal indications requiring high mucosal drug exposure."

Findings relevant to UC include:

- **High colon exposure:** TTI-101 achieved approximately 8-fold higher drug levels in the colon than in plasma, indicating accumulation in the target organ, at pharmacologically relevant levels for inhibition of STAT3-dependent proliferation.
- **Broad effects on disease-associated gene expression:** TTI-101 reversed many disease-induced changes in colon gene expression, including genes associated with colorectal cancer and STAT3 signaling. The normalized genes span the principal axes of UC biology: regulators of cellular immune responses, including recognized IBD/UC susceptibility genes, components of the humoral immune response, inflammatory and acute-phase mediators and epithelial-barrier and proliferative genes. Normalizing gene expression across these interacting programs, rather than blocking a single mediator, supports the potential of STAT3 inhibition to interrupt the chronic disease process.
- **TTI-101 prevented tumors from forming:** TTI-101 prevented adenocarcinoma formation entirely ($p \leq 0.05$), while pY-STAT3 (activated STAT3) was found to be elevated in the tumors that developed in vehicle-treated animals. TTI-101 reached levels more than 20 times the STAT3 IC_{50} (the concentration needed to block STAT3-driven growth) in the colon.

  These prevention results build on earlier work in the chronic AOM-DSS treatment model[1], in which TTI-101, given as treatment after colitis was established, achieved high drug exposure in the colon and statistically significantly reduced tumor formation.

Addressing the chronic nature of UC: UC is a chronic, relapsing disease driven by three linked, STAT3-regulated processes:

immune dysregulation, inflammation and proliferation. Current advanced therapies are directed primarily at inflammation, and placebo-adjusted clinical remission rates remain below 30%. Genetic and pharmacologic studies have implicated activated STAT3 in the severity of colitis; pY-STAT3 inhibition has shown activity across both short- and long-term treatment settings. In three acute models representing distinct immune axes of UC, TTI-101/TTI-109 statistically significantly reduced immune dysregulation, diarrhea, colonic inflammation, colon shortening and pY-STAT3 in the colon. In the longer-term AOM-DSS model, TTI-101 demonstrated activity after colitis was established. In the present study, after ten weeks of continuous dosing in mouse models, TTI-101 sustained normalization of the colon transcriptome and prevented the development of colon adenocarcinomas, a long-term consequence of chronic colitis. Across Tvardi's clinical data, STAT3 inhibition modulated the same three-part signature: reduced key immune cell populations in healthy volunteers, reduced IL-6, a central pro-inflammatory cytokine that signals through STAT3, and reduced fibrosis score in patients with idiopathic pulmonary fibrosis. Taken together, these findings suggest the potential for STAT3 inhibition to act on the underlying biology leading to and driving the chronic nature of UC.

"Building on our experience with TTI-101, we developed TTI-109 as a next-generation prodrug designed to preserve TTI-101's STAT3-targeting mechanism while improving drug delivery and tolerability. Our recently completed Phase 1 healthy volunteer study of TTI-109 demonstrated predictable pharmacokinetics, favorable GI tolerability and modulation of UC-relevant immune cell populations, which we believe further supports our development in UC," Dr. Alibhai concluded.

The publication can be found here.

1. Robinson P, et al. STAT3 Inhibition to Treat Ulcerative Colitis-Associated Colorectal Cancer. *Int J Mol Sci*. 2025;26(21):10808.

About Tvardi Therapeutics

Tvardi is a clinical-stage biopharmaceutical company focused on the development of novel, oral small molecule therapies targeting STAT3 to treat inflammatory and proliferative diseases with significant unmet need. STAT3 is a central mediator across critical signaling pathways that drive uncontrolled proliferation, survival and immune dysregulation. STAT3 is also positioned at the intersection of many signaling pathways integral to the survival and immune evasion of cancer cells. The Company has completed a Phase 1 healthy volunteer study of TTI-109 and plans to initiate clinical trials of TTI-109 in gastrointestinal (GI) diseases pending IND clearance and the availability of additional funding. The Company is also conducting a Phase 1b/2 clinical trial of TTI-101 in hepatocellular carcinoma (NCT05440708). To learn more, please visit tvarditherapeutics.com or follow us on LinkedIn and X (Twitter).

Contacts:

For Tvardi:
Tvardi Investor Relations
ir@tvardi.com

PJ Kelleher
LifeSci Advisors
617-430-7579
pkelleher@lifesciadvisors.com

Cautionary Statement Regarding Forward-looking Statements

Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the anticipated benefits of Tvardi's product candidates, including TTI-101 and TTI-109 in UC and of the Company's STAT3 inhibitors, including in modulating underlying UC disease biology; the potential benefits of TTI-109 as compared to TTI-101, including improved delivery and tolerability; its ongoing and planned clinical trials; the results from preclinical models of UC supporting the advancement of TTI-101 and TTI-109 into future clinical trials; the Company's plans to develop TTI-109 in UC; and other statements regarding management's intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them.

Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. These forward-looking statements are subject to a number of risks, including, among other things: the uncertainties associated with Tvardi's product candidates, as well as risks associated with the clinical development and regulatory approval of product candidates, including potential delays in the completion of clinical trials or safety or other complications related to its product candidates; the ability to replicate the positive results from preclinical studies or early clinical trials in future clinical trials; the ability to obtain IND clearance for TTI-109 in GI therapeutic areas on the timelines expected or at all; the requirement for additional capital to continue to advance these product candidates, which may not be available on favorable terms or at all; the significant net losses Tvardi has incurred since inception; Tvardi's ability to initiate and complete ongoing and planned preclinical studies and clinical trials and advance its product candidates through clinical development; the timing of the availability of data from Tvardi's clinical trials; the outcome of preclinical testing and clinical trials of Tvardi's product candidates, including the ability of those trials to satisfy relevant governmental or regulatory requirements; Tvardi's plans to research, develop and commercialize its current and future product candidates; the clinical utility, potential

benefits and market acceptance of Tvardi's product candidates; the estimated patient populations and total addressable markets for the indications in which Tvardi seeks to develop its product candidates; Tvardi's anticipated cash runway; Tvardi's ability to attract, hire, and retain skilled executive officers and employees; Tvardi's ability to protect its intellectual property and proprietary technologies; Tvardi's reliance on third parties, contract manufacturers and contract research organizations; the possibility that Tvardi may be adversely affected by other economic, business or competitive factors; risks associated with changes in applicable laws or regulations; those factors discussed in Tvardi's filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Annual Report on Form 10-K for the year ended December 31, 2025, and Tvardi's other documents subsequently filed with or furnished to the SEC, all of which are available on the SEC's website at www.sec.gov. All forward-looking statements contained in this press release speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.