Tvardi Announces Publication of First-in-Human Study of TTI-101

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Tvardi's previously announced merger with publicly traded Cara Therapeutics is on-track to close in 1H 2025

TTI-101 is currently being evaluated in a Phase 2 study in patients with idiopathic pulmonary fibrosis (REVERT IPF) and a Phase 2 study in patients with hepatocellular carcinoma (REVERT LIVER CANCER)

Houston, TX – March 19, 2025 – Tvardi Therapeutics, Inc. ("Tvardi"), a clinical-stage biopharmaceutical company developing novel STAT3 inhibitors for fibrosis-driven diseases, announced today that results from the first-in-human Phase 1 study of TTI-101 in patients with advanced solid tumors have been published in the journal *Clinical Cancer Research*.

Imran Alibhai, Ph.D., Chief Executive Officer of Tvardi Therapeutics, stated, "The positive results of this Phase 1 study speak to the potential broad clinical utility of our lead candidate, TTI-101, across a range of fibrosis-driven diseases in which STAT3-mediated proliferation is implicated. Perhaps most notable, in addition to its biological activity in advanced treatment-refractory hepatocellular carcinoma, was a pharmacodynamic reduction of TTI-101's target, activated STAT3, within paired tumor biopsies. We believe these findings provide very strong rationale for our ongoing Phase 2 studies in IPF and liver cancer."

The publication, titled, "Phase 1 Trial of TTI-101, a First-in-Class Oral Inhibitor of STAT3, in Patients with Advanced Solid Tumors," describes a Phase 1 study in which patients, who received a median of three prior systemic therapies, were treated with TTI-101 monotherapy orally twice daily (**NCT03195699**). By targeting both intrinsic tumorigenesis and extrinsic immune suppression, TTI-101 showed promising antitumor activity across tumor types, particularly in patients with hepatocellular carcinoma who were refractory to immune checkpoint inhibitors and anti-angiogenic agents.

TTI-101 showed dose-linear pharmacokinetics and, at the recommended Phase 2 dose, the trough exposure levels were above the IC_{90} for STAT3-induced growth. No dose-limiting toxicities or treatment-related adverse events greater than grade 3 were observed. Pharmacodynamic analysis demonstrated TTI-101 decreased levels of phosphotyrosine (pY) STAT3 within paired tumor biopsies. The paper can be found **here**.

About Tvardi Therapeutics
Tvardi is a clinical stage, biopharmaceutical company focused on the discovery and development of oral, small molecule therapies targeting STAT3 to treat fibrosis-driven diseases. STAT3 is a central mediator across critical fibrotic signaling pathways that drive uncontrolled deposition, proliferation, survival and immune suppression. STAT3 is also positioned at the intersection of many signaling pathways integral to the survival and immune evasion of cancer cells. The company is conducting Phase 2 clinical trials in fibrosis-driven diseases with high unmet need: idiopathic pulmonary fibrosis (**NCT05671835**) and hepatocellular carcinoma (**NCT05440708**). To learn more, please visit **tvardi.com** or follow us on **LinkedIn** and **X (Twitter)**.

No Offer or Solicitation
This communication shall not constitute an offer to sell or the solicitation of an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sale of securities in any jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such jurisdiction. No public offer of securities shall be made except by means of a prospectus meeting the requirements of Section 10 of the Securities Act of 1933, as amended.

Proposed Merger
In connection with the **previously announced** proposed transaction between Cara Therapeutics, Inc. ("Cara") and Tvardi, Cara has filed with the Securities and Exchange Commission ("SEC") a registration statement on Form S-4 that contains a proxy statement and prospectus, which was declared effective on February 14, 2025, and intends to file other relevant materials with the SEC in connection with such proposed transaction. CARA AND TVARDI URGE INVESTORS AND STOCKHOLDERS TO READ THESE MATERIALS CAREFULLY AND IN THEIR ENTIRETY BECAUSE THEY CONTAIN OR WILL CONTAIN IMPORTANT INFORMATION ABOUT CARA, TVARDI, THE PROPOSED TRANSACTION AND RELATED MATTERS. Stockholders will be able to obtain free copies of the proxy statement, prospectus and other documents filed by Cara with the SEC (when they become available) through the website maintained by the SEC at www.sec.gov. In addition, stockholders will be able to obtain free copies of the proxy statement, prospectus and other documents filed by Cara with the SEC by contacting Investor Relations by email at investor@caratherapeutics.com. Stockholders are urged to read the proxy statement, prospectus and the other relevant materials when they become available before making any voting or investment decision with respect to the proposed transaction.

Participants in the Solicitation
Cara and Tvardi, and each of their respective directors and executive officers and certain of their other members of management

and employees, may be deemed to be participants in the solicitation of proxies in connection with the proposed transaction. Information about Cara's directors and executive officers, consisting of Helen M. Boudreau, Jeffrey L. Ives, Ph.D., Christopher Posner, Susan Shiff, Ph.D., Martin Vogelbaum, Lisa von Moltke, M.D., Ryan Maynard and Scott Terrillion, including a description of their interests in Cara, by security holdings or otherwise, can be found under the captions, "Principal Stockholders of Cara," and "Cara's Director and Executive Compensation" contained in the proxy statement/prospectus that is included in the registration statement on Form S-4 (File No. 333-283900) that was declared effective on February 14, 2025 (the "Cara Registration Statement"). To the extent that Cara's directors and executive officers and their respective affiliates have acquired or disposed of security holdings since the applicable "as of" date disclosed in the Cara Registration Statement, such transactions have been or will be reflected on Statements of Change in Beneficial Ownership on Form 4 filed with the SEC. Additional information regarding the persons who may be deemed participants in the proxy solicitation, including the information about the directors and executive officers of Tvardi, and a description of their direct and indirect interests, by security holdings or otherwise, are also included in the Cara Registration Statement. Investors should read the registration statement, proxy statement/prospectus and the other relevant materials before making any voting or investment decision with respect to the proposed transaction. These documents can be obtained free of charge from the sources indicated above

Cautionary Statement Regarding Forward-Looking Statements
Certain statements contained in this communication regarding matters that are not historical facts, are forward-looking statements within the meaning of Section 21E of the Securities and Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995, known as the PSLRA. These include statements regarding the anticipated completion and effects of the proposed merger and related timing, Tvardi's and the combined company's planned clinical programs, including planned clinical trials and the timing for data readouts, the potential of Tvardi's product candidates, including the potential broad clinical utility of TTI-101, the results from the Phase 1 study of TTI-101 providing a strong rationale for Tvardi's ongoing Phase 2 studies, 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.

No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Cara and Tvardi undertake no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise, except to the extent required by law. We use words such as "anticipates," "believes," "plans," "expects," "projects," "future," "intends," "may," "will," "should," "could," "estimates," "predicts," "potential," "continue," "guidance," and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions of the PSLRA. Such forward-looking statements are based on our expectations and involve risks and uncertainties; consequently, actual results may differ materially from those expressed or implied in the statements due to a number of factors, including, but not limited to, risks relating to the completion of the merger, including the need for stockholder approval and the satisfaction of closing conditions. Risks and uncertainties related to Tvardi that may cause actual results to differ materially from those expressed or implied in any forward-looking statement include, but are not limited to: Tvardi's plans to develop and commercialize its product candidates, including TTI-101; the timing of completion of Tvardi's planned clinical trials; the timing of the availability of data from Tvardi's clinical trials; the clinical utility, potential benefits and market acceptance of TTI-101; the ability to replicate the positive results from Tvardi's early clinical trials in future clinical trials; Tvardi's commercialization, marketing and manufacturing capabilities and strategy; Tvardi's ability to identify additional products or product candidates with significant commercial potential; the impact of government laws and regulations; Tvardi's ability to protect its intellectual property position; and Tvardi's estimates regarding future revenue, expenses, capital requirements and need for additional financing following the proposed transaction.

New factors emerge from time to time, and it is not possible for us to predict all such factors, nor can we assess the impact of each such factor on the business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. These risks, as well as other risks associated with the merger, are more fully discussed in the Cara Registration Statement. Additional risks and uncertainties are identified and discussed in the "Risk Factors" section of Cara's Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and other documents filed from time to time with the SEC. Forward-looking statements included in this release are based on information available to Cara and Tvardi as of the date of this release. Neither Cara nor Tvardi undertakes any obligation to update such forward-looking statements to reflect events or circumstances after the date of this release, except to the extent required by law.

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