Zymeworks Announces FDA Clearance of Investigational New Drug Application for ZW251, a Novel Glypican 3-Targeted Topoisomerase 1 Inhibitor Antibody-Drug Conjugate

July 28, 2025

- *Second antibody-drug conjugate (ADC) to progress into clinical development utilizing our proprietary payload and optimized antibody*
- *Preclinical results demonstrate strong anti-tumor activity and favorable tolerability profile*
- *Phase 1 clinical trial evaluating ZW251 in hepatocellular carcinoma (HCC) expected to be initiated in 2025*

VANCOUVER, British Columbia, July 28, 2025 (GLOBE NEWSWIRE) -- Zymeworks Inc. (Nasdaq: ZYME), a clinical-stage biotechnology company developing a diverse pipeline of novel, multifunctional biotherapeutics to improve the standard of care for difficult-to-treat diseases, including cancer, inflammation, and autoimmune disease, today announced the U.S. Food and Drug Administration (FDA) has cleared the investigational new drug (IND) application for ZW251, a novel glypican-3 (GPC3)-targeted ADC incorporating the company's proprietary topoisomerase 1 inhibitor (TOPO1i) payload, ZD06519, for the treatment of HCC.

HCC is the most common type of primary liver cancer, with GPC3 expressed in over 75% of cases[1]. ZW251 is a potential first-in-class ADC engineered to selectively target GPC3. It is composed of a humanized IgG1 antibody conjugated to a novel camptothecin-based TOPO1i using a validated peptide cleavable linker. A drug-antibody-ratio (DAR) of four was selected for ZW251 as a lower DAR potentially could unlock a broader range of dose levels, a potential benefit as HCC patients are commonly challenged by impairment of liver function as a result of chronic liver disease and cirrhosis. In preclinical studies, ZW251 demonstrated strong activity in a range of HCC models, including a range of patient derived xenografts exhibiting a breadth of GPC3 expression and noteworthy tolerability in non-human primate toxicology studies at doses up to 120 mg/kg.

"This advancement marks the second ADC from our wholly-owned pipeline, utilizing our proprietary TOPO1i payload, to progress into clinical development, reinforcing confidence in our approach," said Paul Moore, Ph.D., Chief Scientific Officer of Zymeworks. "Like ZW191, which is currently in clinical trials, ZW251 utilizes the same payload paired with an optimized antibody. Our observations with ZW191 in the clinic to date provide a strong foundation as we initiate clinical development of this second ADC. With its novel design, unique mechanism of action, and promising preclinical activity, ZW251 offers the potential to meaningfully improve upon the current standard of care for HCC either as a monotherapy or in combination."

We plan to commence Phase 1 clinical studies for ZW251 in 2025.

About Zymeworks Inc.
Zymeworks is a global clinical-stage biotechnology company committed to the discovery, development, and commercialization of novel, multifunctional biotherapeutics. Zymeworks' mission is to make a meaningful difference in the lives of people impacted by difficult-to-treat conditions such as cancer, inflammation, and autoimmune disease. The Company's complementary therapeutic platforms and fully integrated drug development engine provide the flexibility and compatibility to precisely engineer and develop highly differentiated antibody-based therapeutic candidates. Zymeworks engineered and developed zanidatamab, a HER2-targeted bispecific antibody using the Company's proprietary Azymetric™ technology. Zymeworks has entered into separate agreements with BeOne Medicines Ltd. (formerly BeiGene, Ltd.) and Jazz Pharmaceuticals Ireland Limited, granting each exclusive rights to develop and commercialize zanidatamab in different territories. The U.S. FDA granted accelerated approval and China' s NMPA granted conditional approval for zanidatamab to treat adults with previously-treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer. The European Commission (EC) has granted conditional marketing authorization for Ziihera® as monotherapy for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC 3+) biliary tract cancer previously treated with at least one prior line of systemic therapy. Zanidatamab is the first and only dual HER2-targeted bispecific antibody approved for HER2-positive biliary tract cancer in the U.S., Europe, and China. In addition, zanidatamab is being evaluated in multiple global clinical trials as a potential best-in-class treatment for patients with multiple HER2-expressing cancers. Zymeworks is rapidly advancing a robust pipeline of wholly-owned product candidates, leveraging its expertise in both antibody-drug conjugates and multispecific antibody therapeutics targeting novel pathways in areas of significant unmet medical need. Phase 1 studies for ZW171 and ZW191 are actively recruiting and ZW251 is expected to enter clinical trials in 2025. In addition to Zymeworks' pipeline, its therapeutic platforms have been further leveraged through strategic partnerships with global biopharmaceutical companies. For information about Zymeworks, visit www.zymeworks.com and follow @ZymeworksInc on X.

Cautionary Note Regarding Forward-Looking Statements
This press release includes "forward-looking statements" or information within the meaning of the applicable securities legislation, including Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements in this press release include, but are not limited to, statements that relate to the efficacy and safety of zanidatamab and Zymeworks' product candidates; ongoing clinical studies and regulatory reviews; the potential addressable market of zanidatamab and Zymeworks' product candidates; the timing of and results of interactions with regulators; Zymeworks' clinical development of its product candidates and enrollment in its clinical trials; the timing and

status of ongoing and future studies, clinical trials and the related data; expectations regarding future regulatory filings and approvals and the timing thereof; potential safety profile and therapeutic effects of zanidatamab and Zymeworks' product candidates; and the commercial potential of technology platforms and product candidates. When used herein, words such as "plan", "believe", "expect", "may", "anticipate", "potential", "will", "intend", "continues", "progress", and similar expressions are intended to identify forward-looking statements. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements are based upon Zymeworks' current expectations and various assumptions. Zymeworks believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain. Zymeworks may not realize its expectations, and its beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of various factors, including, without limitation: clinical trials, including any required confirmatory trials, may not demonstrate safety and efficacy of any of Zymeworks' or its collaborators' product candidates; any of Zymeworks' or its partners' product candidates may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; conditional regulatory approval may be withdrawn or revoked if any of Zymeworks' or its partners' product candidates fail to satisfy the requirements of any such conditional regulatory approvals; regulatory agencies may impose additional requirements or delay the initiation of clinical trials; the impact of new or changing laws and regulations; market conditions, including the impact of tariffs; potential negative impacts of FDA regulatory delays and uncertainty and new policies implemented under the current administration, including executive orders, changes in the leadership of federal agencies such as the FDA, staff layoffs, budget cuts to agency programs and research, and changes in drug pricing controls; the impact of pandemics and other health crises on Zymeworks' business, research and clinical development plans and timelines and results of operations, including impact on its clinical trial sites, collaborators, and contractors who act for or on Zymeworks' behalf; zanidatamab and Zymeworks' product candidates may not be successfully commercialized; clinical trials and any future clinical trials may not demonstrate safety and efficacy of any of Zymeworks' or its collaborators' product candidates; inability to maintain or enter into new partnerships or strategic collaborations; and the factors described under "Risk Factors" in Zymeworks' quarterly and annual reports filed with the Securities and Exchange Commission (copies of which may be obtained at www.sec.gov and www.sedarplus.ca).

Although Zymeworks believes that such forward-looking statements are reasonable, there can be no assurance they will prove to be correct. Investors should not place undue reliance on forward-looking statements. The above assumptions, risks and uncertainties are not exhaustive. Forward-looking statements are made as of the date hereof and, except as may be required by law, Zymeworks undertakes no obligation to update, republish, or revise any forward-looking statements to reflect new information, future events or circumstances, or to reflect the occurrences of unanticipated events.

Contacts:

Investor Inquiries:
Shrinal Inamdar
Senior Director, Investor Relations
(604) 678-1388
ir@zymeworks.com

Media Inquiries:
Diana Papove
Senior Director, Corporate Communications
(604) 678-1388
media@zymeworks.com

---

[1] Wang HL et al., Arch Pathol Lab Med 2008.

Source: Zymeworks Inc.