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Leap Therapeutics Presents Final Data from DeFianCe Study at ESMO 2025

October 20, 2025

Sirexatamab demonstrated statistically significant improvement in PFS and OS in DKK1-high population

Increasing DKK1 levels further improved PFS, OS, and ORR advantage for the Sirexatamab Arm

Leap to continue supporting development of sirexatamab in DKK1-high CRC patients

CAMBRIDGE, Mass., Oct. 20, 2025 /PRNewswire/ -- Leap Therapeutics, Inc. (Nasdaq:LPTX), a biotechnology company focused on developing targeted and immuno-oncology therapeutics, today announced final results from Part B of the DeFianCe study (NCT05480306), a Phase 2 study of sirexatamab (DKN-01), an anti-DKK1 monoclonal antibody, in combination with bevacizumab and chemotherapy (Sirexatamab Arm) compared to bevacizumab and chemotherapy (Control Arm) in patients with microsatellite stable (MSS) colorectal cancer (CRC) who have received one prior systemic therapy for advanced disease. The final clinical results were presented on behalf of the DeFianCe study investigators by Zev Wainberg, MD, Professor of Medicine and Co-Director of the GI Oncology Program at UCLA in a Mini Oral session at the European Society for Medical Oncology (ESMO) Congress 2025 in Berlin, Germany.

"Circulating DKK1 is a negative prognostic factor and elevated in patients with advanced, metastatic CRC. The data presented at ESMO demonstrate that sirexatamab, which binds to and removes free DKK1, has significant potential to provide a survival benefit for CRC patients who have high DKK1 levels and who are likely to have poor outcomes receiving the current standard of care alone," said Dr. Wainberg. "Sirexatamab has the potential to be a valuable addition to the CRC treatment paradigm as a targeted therapeutic for patients with high DKK1 and should move forward to be evaluated in a biomarker-focused registrational trial."

The DeFianCe study was a two part, open-label, multi-country study. Part A of the DeFianCe study enrolled 33 patients, including a significant number of patients who had early progression on first-line therapy, previous exposure to bevacizumab, tumors with RAS mutations, or liver and lung metastases. The study expanded into a 188 patient Part B randomized controlled trial. The primary objective of the study was progression-free survival PFS. Secondary objectives included objective response rate (ORR), duration of response, and overall survival (OS). A key pre-defined exploratory population was those patients who had high levels of circulating DKK1, as measured by a biomarker assay.

Key Part B DeFianCe Study Findings:

- Across the DKK1-high (upper median) patients (n=88):
  - ORR was 38.0% in the Sirexatamab Arm compared to 23.7% ORR in the Control Arm.
  - mPFS was 9.03 months in the Sirexatamab Arm compared to 7.06 months in the Control Arm, Hazard Ratio (HR) 0.61, p-value = 0.0255.
  - mOS was not reached in the Sirexatamab Arm compared to 14.39 months in the Control Arm, HR 0.42, p-value = 0.0118.
- Across the DKK1-high (upper quartile) patients (n=44):
  - ORR was 44.0% in the Sirexatamab Arm compared to 15.8% ORR in the Control Arm.
  - mPFS was 9.36 months in the Sirexatamab Arm compared to 5.88 months in the Control Arm, HR 0.46, p-value = 0.0168.
  - mOS was not reached in the Sirexatamab Arm compared to 9.66 months in the Control Arm, HR 0.17, p-value < 0.001.
- In the full intent-to-treat population (n=188):
  - ORR was 35.1% in the Sirexatamab Arm compared to 26.6% ORR in the Control Arm.
  - mPFS was 9.2 months in the Sirexatamab Arm compared to 8.3 months in the Control Arm, HR 0.84, p-value = 0.1712.
  - Event-free rate favors Sirexatamab Arm beginning at month 9 (53 vs 47%) with further separation at month 12 (34 vs 23%).
- Sirexatamab, in combination with chemotherapy and bevacizumab, was safe and well tolerated
  - Overall treatment-emergent adverse effects (TEAE) profile was similar between the Sirextamab and Control Arms, suggesting sirexatamab did not impact the safety profile when combined with the standard of care.

"The DeFianCe study results demonstrate the significant potential of sirexatamab in patients with advanced CRC. Patients with this aggressive cancer, particularly those with high DKK1 levels, have poor overall survival outcomes and few promising second-line or later options," said Douglas E. Onsi, President and Chief Executive Officer of Leap. "Sirexatamab has repeatedly demonstrated its potential as a novel, first-in-class antibody targeting DKK1 that provides deep and durable benefit for patients in desperate need of new therapies. With support from a recently completed financing, Leap plans to engage with regulatory authorities over the registrational path for sirexatamab in CRC and to optimize the DKK1 biomarker diagnostic test that could be used to identify these CRC patients with poor prognosis."

About Leap Therapeutics
Leap Therapeutics (Nasdaq: LPTX) is focused on developing targeted and immuno-oncology therapeutics. Leap's pipeline includes sirexatamab (DKN-01), a humanized monoclonal antibody targeting the Dickkopf-1 (DKK1) protein, and FL-501, a humanized monoclonal antibody targeting the

growth and differentiation factor 15 (GDF-15) protein. Leap initiated a digital asset treasury strategy following a $58.88 million private placement led by Winklevoss Capital, aiming to build long-term shareholder value and continue the development of sirexatamab and FL-501. For more information about Leap Therapeutics, visit http://www.leaptx.com or view our public filings with the SEC that are available via EDGAR at http://www.sec.gov or via https://investors.leaptx.com/.

FORWARD-LOOKING STATEMENTS

This press release includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, Section 21E of the Securities Exchange Act of 1934, as amended. These forward-looking statements generally can be identified by the use of words such as "anticipate," "expect," "plan," "could," "may," "will," "believe," "estimate," "forecast," "goal," "project," and other words of similar meaning. These forward-looking statements, including statements regarding the potential safety, efficacy, and regulatory and clinical progress of sirexatamab; regulatory feedback that Leap may receive from U.S. Food and Drug Administration (FDA) or equivalent foreign regulatory agency or from site institutional review boards; the intended use of proceeds from the recent private placement offering; the assets to be held by the Company; the expected future market, price and liquidity of the digital assets the Company acquires; the macro and political conditions surrounding digital assets; and the Company's plan for value creation and performance. Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others, any regulatory feedback that Leap may receive from FDA or equivalent foreign regulatory agency or from site institutional review boards; failure to realize the anticipated benefits of the digital asset treasury strategy; changes in business, market, financial, political and regulatory conditions; risks relating to the Company's operations and business, including the highly volatile nature of the price of cryptocurrencies; the risk that the price of the Company's common stock may be highly correlated to the price of the digital assets that it holds; risks related to increased competition in the industries in which the Company does and will operate; risks relating to significant legal, commercial, regulatory, and technical uncertainty regarding pharmaceutical development and digital assets generally; and risks relating to the treatment of crypto assets for U.S. and foreign tax purposes. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements. Leap may not actually achieve the forecasts disclosed in such forward-looking statements, and you should not place undue reliance on such forward-looking statements. Such forward-looking statements are subject to a number of material risks and uncertainties including but not limited to those set forth under the caption "Risk Factors" in Leap's most recent Annual Report on Form 10-K filed with the SEC, as well as discussions of potential risks, uncertainties, and other important factors in its subsequent filings with the SEC. Any forward-looking statement speaks only as of the date on which it was made. Neither Leap, nor any of its affiliates, advisors or representatives, undertake any obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law. These forward-looking statements should not be relied upon as representing Leap's views as of any date subsequent to the date hereof.

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