Foghorn Therapeutics Presents New Preclinical Data on Selective SMARCA2 Inhibitor FHD-909 and Selective CBP and Selective EP300 Degrader Programs and Provides Pipeline Update

Apr 28, 2025

- FHD-909 (LY4050784) advancing in Phase 1 trial in SMARCA4 (BRG1) mutated cancers, with non-small cell lung cancer (NSCLC) as the primary target population

- Preclinical synergistic anti-tumor activity of FHD-909 in combination with pembrolizumab and KRAS inhibitors supports clinical exploration

- Selective CBP degrader combination approaches show promise in preclinical ER+ breast cancer models

- Further preclinical characterization of the therapeutic potential of the Selective EP300 degrader program to treat advanced hematological malignancies

Virtual investor event Tuesday, April 29, 2025, at 8 a.m. ET

CAMBRIDGE, Mass., April 28, 2025 (GLOBE NEWSWIRE) -- Foghorn® Therapeutics Inc. (Nasdaq: FHTX), a clinical-stage biotechnology company pioneering a new class of medicines that treat serious diseases by correcting abnormal gene expression, today announced new preclinical data for potential first-in-class medicines, including FHD-909, a SMARCA2 (BRM) selective inhibitor, and the Selective CBP degrader program at the 2025 American Association for Cancer Research (AACR) Annual Meeting. A poster on the Selective EP300 degrader program will be presented on Wednesday, April 30, 2025. Foghorn management will hold a virtual investor event on Tuesday April 29, 2025, at 8 a.m. ET to review important pipeline updates.

"We are excited by the preclinical combination data of FHD-909, a first-in-class oral selective SMARCA2 inhibitor, with chemotherapy, KRAS inhibitors and pembrolizumab, which support further clinical exploration in NSCLC," said Adrian Gottschalk, President and Chief Executive Officer of Foghorn. "Building on the robust preclinical monotherapy activity we previously reported, new combination data was presented as part of an oral presentation at this year's AACR annual meeting. Enrollment and dose escalation continue in the ongoing Phase 1 trial evaluating FHD-909. We look forward to continued progress on our FHD-909 program in collaboration with Lilly."

Mr. Gottschalk continued, "For our Selective CBP degrader program, we presented initial preclinical data defining combination opportunities that support potential beyond EP300-mutant cancers, including data in ER+ breast cancer. On Wednesday this week, we will present preclinical findings further characterizing the therapeutic potential of our Selective EP300 degrader program to treat hematological malignancies. And tomorrow during our investor event, we will provide an overview of our Selective ARID1B degrader program, a synthetic lethal target implicated in up to 5% of all solid tumors, to set the stage for a program update expected in the second half of the year. It has been a productive start to 2025, and we look forward to continued progress over the next 12 months."

Presentation Highlights

FHD-909 (LY4050784) Program – In Collaboration with Lilly

Oral Presentation Title: LY4050784, a Selective Inhibitor of SMARCA2, Demonstrates Synergistic Activity in Combinations with Pembrolizumab or KRAS Inhibitors

Enhanced anti-tumor activity with FHD-909 in combination with standard-of-care chemotherapies, anti-PD-1 pembrolizumab and several novel KRAS inhibitors in NSCLC animal models warrants clinical exploration. Selectively blocking SMARCA2 activity is a promising synthetic lethal strategy intended to induce tumor death while sparing healthy cells. SMARCA4 is mutated in up to 10% of NSCLC alone and frequently co-occurs with KRAS mutations, resulting in poor clinical outcomes upon treatment with KRAS or checkpoint inhibitors.

- FHD-909 monotherapy selectively inhibits SMARCA4 mutant cancer cells *in vitro*, is well tolerated, and demonstrates robust anti-tumor efficacy in SMARCA4 mutant NSCLC xenograft models
- FHD-909 shows additive activity with standard-of-care chemotherapies (platinum, paclitaxel, pemetrexed, gemcitabine and docetaxel) and synergistic activity in multiple combinations including KRAS G12C, KRAS G12D, and pan-KRAS inhibitors, as well as anti-PD-1 pembrolizumab
- Findings support further clinical exploration

Poster Presentation Title: A First-in-human Phase 1 Study of LY4050784, an Oral, Potent, and Selective SMARCA2

Inhibitor, in Patients with Advanced Solid Tumors with SMARCA4 Alterations (Trial in Progress)

FHD-909 is a potential first-in-class, highly selective SMARCA2 inhibitor in ongoing Phase 1 evaluation in patients with SMARCA4 mutations who have exhausted standard treatment options.
Newly diagnosed patients with SMARCA4 mutated NSCLC have worse prognosis and shorter survival (median overall survival 8 vs. 15 months) compared to their wild-type counterparts (*Alessi JV, et al., 2021*). Selectively blocking the enzymatic activity of SMARCA2 is a promising synthetic lethal strategy intended to induce tumor death while sparing healthy cells. FHD-909 is a first-in-class oral, selective SMARCA2 inhibitor with high selectivity over its closely related paralog SMARCA4.

- First-in-human trial of FHD-909 will evaluate patients with SMARCA4 mutated locally advanced or metastatic solid tumors who have exhausted standard treatment options
- Upon completion of the dose escalation part of the study, two separate expansion cohorts will enroll either patients with NSCLC or with other advanced solid tumors harboring eligible SMARCA4 alteration(s)

Selective CBP Degrader Program

Poster Presentation Title: Establishing Rational Combination Strategies with Selective CBP Degraders in Solid Tumor Indications

Selective CBP degraders have combinatorial benefit with approved chemotherapies and targeted agents in solid tumors beyond EP300-mutant cancers. CBP and EP300 are highly similar acetyltransferases that share a bi-directional synthetic lethal relationship but are challenging to drug independently, and dual inhibition is associated with dose-limiting toxicities. Previously, we showed our selective CBP degraders have potent antiproliferative activity in EP300-mutant cancers.

- Synergistic combination activity demonstrated, including with paclitaxel and CDK4/6 inhibitor abemaciclib in ER+ breast cancer
- Findings support combination opportunities for selective CBP degraders in solid tumors beyond EP300-mutant cancers

Selective EP300 Degrader Program

Poster Title: Anti-cancer Activity of Potent and Selective EP300 Degradation in Hematological Malignancies (Presentation on Wednesday April 30, 2025)

A potent and selective heterobifunctional degrader of EP300 has significant preclinical activity in hematological malignancies. Historically, selectively drugging EP300 has been challenging due to the high similarity between EP300 and CBP, while dual inhibition of CBP/EP300 has been limited by dose limiting toxicities. EP300 lineage dependencies are further characterized in multiple myeloma and diffuse large B cell lymphoma (DLBCL).

- Anti-proliferative activity in a broad range of hematological malignancies *in vitro*, including DLBCL, multiple myeloma, and follicular lymphoma
- Achieved *in vivo* efficacy in the Karpas422 germinal center B-cell-like (GCB)-DLBCL xenograft model
- No thrombocytopenia observed in mice at efficacious doses
- Targeted selective EP300 degradation shows promise as a well-tolerated and effective treatment strategy to treat advanced hematological malignancies

Selective ARID1B Degrader Program

Investor Event: Selective ARID1B Degrader Program Overview

Successfully developing potent and selective degraders of ARID1B. ARID1B is a major synthetic lethal target implicated in up to 5% of all solid tumors. Attempts to selectively drug ARID1B have been challenging because of the high degree of similarity between ARID1A and ARID1B and the lack of enzymatic activity to target.

- Developed highly potent and selective binders to ARID1B
- Achieved selective degradation of ARID1B
- Program update expected in 2H 2025

Investor Event Information
Foghorn management will hold a virtual investor event on Tuesday, April 29, 2025, at 8 a.m. ET to review pipeline updates in conjunction with the 2025 American Association for Cancer Research (AACR) Annual Meeting. A live question and answer session will follow the formal presentation. To register for the event, please click here. The live webcast and replay may be accessed under Events and Presentations in the Investors section of Foghorn's website, www.foghorntx.com, and will be available for up to 30 days.

About FHD-909
FHD-909 (LY4050784) is a potent, first-in-class, allosteric and orally available small molecule that selectively inhibits the ATPase activity of SMARCA2 (BRM) over its closely related paralog SMARCA4 (BRG1), two proteins that are the catalytic engines across all forms of the BAF complex, one of the key regulators of the chromatin regulatory system. In preclinical studies, tumors with mutations in SMARCA4 rely on SMARCA2 for BAF function. FHD-909 has shown significant anti-tumor activity across multiple

SMARCA4 mutant lung tumor models.

About Foghorn Therapeutics

Foghorn® Therapeutics is discovering and developing a novel class of medicines targeting genetically determined dependencies within the chromatin regulatory system. Through its proprietary scalable Gene Traffic Control® platform, Foghorn is systematically studying, identifying and validating potential drug targets within the chromatin regulatory system. The Company is developing multiple product candidates in oncology. Visit our website at www.foghorntx.com for more information on the Company, and follow us on X and LinkedIn.

Forward-Looking Statements

This press release contains "forward-looking statements." Forward-looking statements include statements regarding the Company's clinical and pre-clinical programs, including the ongoing Phase 1 trial evaluating FHD-909 in SMARCA4 mutated cancers, selective CBP and selective EP300 degrader programs, selective ARID1B degrader program, the Company's other product candidates and research efforts and other statements identified by words such as "could," "may," "might," "will," "likely," "anticipates," "intends," "plans," "seeks," "believes," "estimates," "expects," "continues," "projects" and similar references to future periods. Forward-looking statements are based on our current expectations and assumptions regarding capital market conditions, our business, the economy and other future conditions. Because forward-looking statements relate to the future, by their nature, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. As a result, actual results may differ materially from those contemplated by the forward-looking statements. Important factors that could cause actual results to differ materially from those in the forward-looking statements include regional, national or global political, economic, business, competitive, market and regulatory conditions, including risks relating to our clinical trials and other factors set forth under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2024, as filed with the Securities and Exchange Commission. Any forward-looking statement made in this press release speaks only as of the date on which it is made.

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