Cogent Biosciences Presents New Preclinical Data Highlighting Potential Best-in-Class Potency and Selectivity of ErbB2 and PI3Kα inhibitor programs at the San Antonio Breast Cancer Symposium

December 7, 2023

Novel EGFR-sparing, brain-penetrant ErbB2 inhibitor demonstrates superior efficacy profile reaching 80% brain penetrance with potent coverage of key mutations inadequately addressed by currently approved therapies

Novel, H1047R mutant-selective PI3Kα inhibitor, disclosed as third Cogent discovery stage program, demonstrates high clinical target engagement without metabolic dysfunction commonly associated with molecules in the class

WALTHAM, Mass. and BOULDER, Colo., Dec. 07, 2023 (GLOBE NEWSWIRE) -- Cogent Biosciences, Inc. (Nasdaq: COGT), a biotechnology company focused on developing precision therapies for genetically defined diseases, today presented updated preclinical data from its potent, selective and brain penetrant ErbB2 inhibitor program along with initial preclinical data from its newly disclosed H1047R mutant-selective PI3Kα inhibitor discovery program at the 2023 San Antonio Breast Cancer Symposium (SABCS), taking place December 5-9, 2023 at the Henry B. González Convention Center in San Antonio, Texas. The posters can be found in the 'Posters and Publications' portion of the Cogent website.

"Broadening our pipeline of potential best-in-class targeted therapies remains key to our long-term strategy, and we are excited to provide an update on our selective, EGFR-sparing ErbB2 inhibitor, which features exceptional potency, half-life and oral bioavailability with potentially best-in-class brain penetrance to enable inhibition of mutations in CNS tissue," said Andrew Robbins, Cogent's President and Chief Executive Officer. "In addition, we are pleased to present initial data on our effort to design a potent H1047R mutant-selective PI3Kα inhibitor. This program aligns with our mission of creating best-in-class targeted therapies for patients with genetically defined diseases and is complementary to our efforts focused on the development of bezuclastinib in advanced and nonadvanced systemic mastocytosis and GIST."

ErbB2 Inhibitor

Presentation ID: PO3-26-02
Title: Identification of a novel, brain penetrant, EGFR sparing, ErbB2 inhibitor with activity against oncogenic ErbB2 mutations
Session: Poster Session 3
Date: Thursday, December 7, 2023
Time: 12:00 PM - 2:00 PM CT (1:00 PM – 3:00 PM ET)

Cogent is developing a potential best-in-class EGFR-sparing, brain-penetrant ErbB2 inhibitor that includes coverage of key mutations (YVMA, S310F, V842I, L755S) inadequately addressed by currently approved therapies. Activating mutations in the ErbB2 gene have been identified in multiple cancers and demonstrate a tumorigenic role similar to that of ErbB2 amplification.

The poster presented today shows that CGT4255 demonstrated low nM potency against ErbB2 wild-type and oncogenic ErbB2 mutations with 100-fold selectivity over wild-type-EGFR. In addition to impressive selectivity across a broad range of kinases, receptors and ion channels, CGT4255 has exceptional half-life in human whole blood and liver cytosol fractions. Dose ascending PK data in mice showed low clearance and high oral bioavailability at all doses, with best-in-class 80% brain penetrance at 100 mg/kg. Maximum inhibition of pErbB2 was observed at a 30 mg/kg PO dose in both NIH/3T3 ErbB2-YVMA and ErbB2-L755S tumor models, with complete regressions at 100 mg/kg PO BID in the NIH3T3 ErbB2-L755S TGI model and was well tolerated. These advances continue to highlight a favorable profile for optimal clinical efficacy.

PI3Kα Inhibitor

Presentation ID: PO3-26-01
Title: Preclinical in vitro and in vivo characterization of a novel, wild-type-sparing, PI3Kα H1047R mutant-selective inhibitor
Session: Poster Session 3
Date: Thursday, December 7, 2023
Time: 12:00 PM - 2:00 PM CT (1:00 PM – 3:00 PM ET)

Cogent is developing a potential best-in-class, wild-type-sparing, PI3Kα inhibitor that provides coverage for the H1047R mutation, which affects >30,000 cancer patients each year. The phosphoinositide 3-kinase (PI3K) pathway is a key cell cycle regulating pathway that has an established role in tumor growth and development. PI3Kα mutations are highly prevalent in many solid tumors and are present in 36% of all breast cancer patients. The approved agents for these patients often lead to dose limitations,

resulting from activity against wild-type PI3Kα.

The poster presented today highlights that CGT4824 is an allosteric inhibitor of PI3K, was well tolerated in the tumor growth inhibition efficacy models and has been profiled as lead series exemplar based on its selectivity for H1047R over WT PI3K. CGT4824 demonstrated low nM potency in H1047R mutant PI3K cell lines, differentiated dose ascending PK in mice with high bioavailability and low clearance. CGT4824 also showed >95% inhibition of pAKT in a H1047R PD model, importantly without increases in insulin or C-peptide. Its efficacy profile was superior to a clinically-relevant dose of alpelisib in the NCI H1048 mouse tumor growth inhibition model. Additional lead series analogs were also described, highlighting our more recent advances toward increasing selectivity and potency against H1047R mutants.

About Cogent Biosciences, Inc.
Cogent Biosciences is a biotechnology company focused on developing precision therapies for genetically defined diseases. The most advanced clinical program, bezuclastinib, is a selective tyrosine kinase inhibitor that is designed to potently inhibit the KIT D816V mutation as well as other mutations in KIT exon 17. KIT D816V is responsible for driving systemic mastocytosis, a serious disease caused by unchecked proliferation of mast cells. Exon 17 mutations are also found in patients with advanced gastrointestinal stromal tumors (GIST), a type of cancer with strong dependence on oncogenic KIT signaling. In addition to bezuclastinib, the Cogent Research Team is developing a portfolio of novel targeted therapies to help patients fighting serious, genetically driven diseases initially targeting mutations in FGFR2, ErbB2 and PI3Ka (genes/pathways). Cogent Biosciences is based in Waltham, MA and Boulder, CO. Visit our website for more information at www.cogentbio.com. Follow Cogent Biosciences on social media: X (formerly known as Twitter) and LinkedIn. Information that may be important to investors will be routinely posted on our website and X.

Forward Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the company's business and operations, as well as the potential benefits of the company's ErbB2 and PI3Kα inhibitor programs. The use of words such as, but not limited to, "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "will," or "would" and similar words expressions are intended to identify forward-looking statements. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our clinical results, the rate of enrollment in our clinical trials and other future conditions. 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. We may not actually achieve the forecasts or milestones disclosed in our forward-looking statements, and you should not place undue reliance on our 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 Cogent's most recent Quarterly Report on Form 10-Q filed with the SEC. Any forward-looking statement speaks only as of the date on which it was made. Neither we, nor our affiliates, advisors or representatives, undertake any obligation to publicly update or revise any forward-looking statement, whether as result of new information, future events or otherwise, except as required by law. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date hereof.

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