Xencor’s IL2-Fc Cytokine, XmAb®564, is Well-tolerated and Selectively Expands Regulatory T Cells in Phase 1a Clinical Study

November 7, 2022

-- Durable, dose-dependent and selective expansion of CD25^{bright} Tregs, reaching a 117-fold increase over baseline at the highest dose --

-- Single dose of XmAb564 well-tolerated with no reported serious adverse events --

-- First patient dosed in Phase 1b, multiple-ascending dose study in patients with atopic dermatitis or psoriasis --

-- Phase 1a results to be presented in a webcast today at 4:30 p.m. ET --

MONROVIA, Calif.--(BUSINESS WIRE)--Nov. 7, 2022-- Xencor, Inc. (NASDAQ:XNCR), a clinical-stage biopharmaceutical company developing engineered antibodies and cytokines for the treatment of cancer and autoimmune diseases, today announced topline clinical data from its Phase 1a single-dose, healthy volunteer study of XmAb®564, in development for patients with autoimmune diseases. XmAb564 is a wholly owned, monovalent interleukin-2 Fc fusion protein (IL-2-Fc), engineered with dramatically lowered potency and heightened binding affinity for the IL-2 alpha receptor (CD25), resulting in selective activation of regulatory T cells (Tregs). Tregs combat autoimmunity by suppressing other immune cells from attacking normal tissue; however, in many autoimmune diseases, Tregs become dysregulated.

“The goal of an IL-2 therapy for autoimmune disease is to provide sustained low-intensity activation of Tregs while avoiding the pro-inflammatory systemic activation of effector T cells,” said John Desjarlais, Ph.D., senior vice president and chief scientific officer at Xencor. “We engineered XmAb564 with heightened affinity for IL-2’s alpha receptor (CD25) over its beta receptor to selectively target Tregs and with 400- to 1000-fold reduced potency to improve the half-life of XmAb564 and reduce its toxicity compared to wildtype IL-2. Fusion to our modular XmAb heterodimeric Fc domain with Xtend™ technology provides a stable protein scaffold and further enhances half-life. XmAb564’s design gave dramatic Treg increases and unprecedented durability for a single dose, with high levels of Treg populations sustained for at least 3 weeks.”

“We have rapidly advanced XmAb564 through a first-in-human study and have now dosed the first patient in a newly initiated Phase 1b, multiple-ascending dose study in patients with atopic dermatitis and psoriasis,” said Allen Yang, M.D., Ph.D., senior vice president and chief medical officer at Xencor. “XmAb564 is the second potency-tuned XmAb cytokine program showing marked target cell expansion and good tolerability in human studies, following XmAb306, our potency-reduced IL-15 in oncology. In addition, XmAb306 showed accumulation of target immune cells upon repeat dosing, which allows study of further extended dosing intervals and helps inform our development of XmAb564.”

The Phase 1 single ascending-dose study of XmAb564 was designed to characterize its safety, tolerability and pharmacokinetics in healthy volunteers, and the study included an analysis of key immunomodulatory biomarkers. The study enrolled 48 subjects, with six dose-level cohorts each randomizing six subjects to XmAb564 and two subjects to placebo. Single doses ranged from 0.003 mg/kg to 0.065 mg/kg.

XmAb564 was well-tolerated across all dose levels. Adverse events (AE) were Grade 1 or Grade 2 and resolved without intervention, and no serious AEs were observed. The most common AE was injection site reaction. Laboratory tests indicated some subjects had transient increases in eosinophils, though no eosinophil-related AEs were observed. This laboratory increase may be related to the mechanism of action of CD25-targeting IL-2 drug candidates.

Dose-dependent and selective expansion of CD25^{bright} and total Tregs was observed throughout the study. The expansion of CD25^{bright} Tregs with at least 10-fold increases over baseline began at the third dose level and reached a 117-fold increase over baseline at the highest dose. Total Tregs increased 8-fold over baseline at the highest dose. An important metric for selectivity, the ratio of Tregs to conventional T cells (which include effector T cells) increased consistently in a dose-dependent manner, with a ratio of 0.14 at the highest dose compared to <0.01 for placebo. Marked elevation of Tregs through at least day 21, exceeding 50 CD25^{bright} Treg cells/µl and 100 total Tregs/µl at the highest dose, provides potentially exceptional durability and supports exploring differentiated multi-week dosing schedules in further clinical studies. Minimal increases in natural killer (NK) cells and conventional T cells (Tcons) were observed.

Conference Call and Webcast

Xencor will host a webcast today at 4:30 p.m. ET (1:30 p.m. PT) to discuss these results, following its quarterly business update and review of financial results. The live webcast will be available under "Events & Presentations" in the Investors section of the Company's website at investors.xencor.com and will be archived for at least 30 days.

About Tregs and IL-2 in Autoimmune Disease

IL-2 is a signaling protein that activates and expands certain immune cell populations, including Tregs. Tregs prevent autoimmunity by suppressing

other immune cells from attacking normal tissue; however, in many autoimmune diseases, Tregs become dysregulated. An existing approach to restore normal immune activity and improve outcomes for patients has been to activate Tregs with IL-2 provided therapeutically at low doses. These regimens, however, suffer from a narrow therapeutic window, because IL-2 is a highly potent molecule that also activates the immune cell populations that Tregs are intended to suppress.

About XmAb®564

XmAb®564 is a wholly owned, monovalent IL-2-Fc fusion protein, engineered to selectively activate and expand Tregs for the potential treatment of patients with autoimmune diseases. XmAb564 is engineered with reduced binding affinity for IL-2's beta receptor (IL-2Rβ, CD122) and increased binding affinity for its alpha receptor (IL-2Rα, CD25). Xencor's XmAb® Bispecific Fc Domain additionally provides a stable protein scaffold and improves XmAb564's pharmacologic properties, and Xencor's Xtend™ Fc technology enhances its circulating half-life. In preclinical studies, XmAb564 was well-tolerated, promoted the selective and sustained expansion of Tregs and exhibited a favorable pharmacokinetic profile.

Xencor is conducting a randomized, double-blind, placebo-controlled, multiple-ascending dose Phase 1b clinical study to evaluate the safety and tolerability of XmAb564, administered subcutaneously in patients with atopic dermatitis and psoriasis.

About Xencor

Xencor is a clinical-stage biopharmaceutical company developing engineered antibodies and cytokines for the treatment of patients with cancer and autoimmune diseases. More than 20 candidates engineered with Xencor's XmAb® technology are in clinical development, and three XmAb medicines are marketed by partners. Xencor's XmAb engineering technology enables small changes to a protein's structure that result in new mechanisms of therapeutic action. For more information, please visit www.xencor.com.

Forward-Looking Statements

Certain statements contained in this press release may constitute forward-looking statements within the meaning of applicable securities laws. Forward-looking statements include statements that are not purely statements of historical fact, and can generally be identified by the use of words such as "potential," "can," "will," "plan," "may," "could," "would," "expect," "anticipate," "seek," "look forward," "believe," "committed," "investigational," and similar terms, or by express or implied discussions relating to Xencor's business, including, but not limited to, statements regarding presentations of clinical data, additional clinical trials, the quotations from Xencor's chief scientific officer and chief medical officer and other statements that are not purely statements of historical fact. Such statements are made on the basis of the current beliefs, expectations, and assumptions of the management of Xencor and are subject to significant known and unknown risks, uncertainties and other factors that may cause actual results, performance or achievements and the timing of events to be materially different from those implied by such statements, and therefore these statements should not be read as guarantees of future performance or results. Such risks include, without limitation, the risks associated with the process of discovering, developing, manufacturing and commercializing drugs that are safe and effective for use as human therapeutics and other risks, including the ability of publicly disclosed preliminary clinical trial data to support continued clinical development and regulatory approval for specific treatments, in each case as described in Xencor's public securities filings. For a discussion of these and other factors, please refer to Xencor's annual report on Form 10-K for the year ended December 31, 2021 as well as Xencor's subsequent filings with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended to date. All forward-looking statements are qualified in their entirety by this cautionary statement and Xencor undertakes no obligation to revise or update this press release to reflect events or circumstances after the date hereof, except as required by law.

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