Akebia Therapeutics Announces Top-Line Results from its PRO2TECT Global Phase 3 Program of Vadadustat for Treatment of Anemia Due to Chronic Kidney Disease in Adult Patients Not on Dialysis

September 3, 2020

- PRO_2TECT achieves primary and key secondary efficacy endpoints

- PRO_2TECT does not meet primary safety MACE endpoint

- Company believes totality of data from global Phase 3 program (PRO_2TECT and $INNO_2$VATE) supports NDA submission for both non-dialysis and dialysis indications

- Company remains on track to submit NDA

- Conference call today at 8:30 a.m. ET

CAMBRIDGE, Mass., Sept. 3, 2020 /PRNewswire/ -- Akebia Therapeutics, Inc. (Nasdaq: AKBA), a biopharmaceutical company with the purpose to better the lives of people impacted by kidney disease, today announces top-line results from PRO_2TECT, the second of its two global Phase 3 cardiovascular outcomes programs. The two PRO_2TECT studies evaluated the efficacy and safety of vadadustat, Akebia's investigational oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), versus darbepoetin alfa for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis. The Company's vadadustat development program also includes two other global Phase 3 studies ($INNO_2$VATE) for the treatment of anemia due to CKD in adult patients on dialysis, for which the Company reported positive top-line data in May.

Vadadustat achieved the primary and key secondary efficacy endpoint in each of the two PRO_2TECT studies, demonstrating non-inferiority (NI) to darbepoetin alfa as measured by a mean change in hemoglobin (Hb) between baseline and the primary evaluation period (weeks 24 to 36) and secondary evaluation period (weeks 40 to 52). Vadadustat did not meet the primary safety endpoint of the PRO_2TECT program, defined as non-inferiority of vadadustat versus darbepoetin alfa in time to first occurrence of major adverse cardiovascular events (MACE), which is the composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke across both PRO_2TECT studies.

Akebia is working to present the full dataset from its global Phase 3 program ($INNO_2$VATE and PRO_2TECT) at an upcoming medical conference and publish the data in peer reviewed journals. Akebia plans to submit to the U.S. Food and Drug Administration (FDA) a New Drug Application (NDA) for vadadustat for the treatment of anemia due to CKD in adult dialysis-dependent and non-dialysis dependent patients as early as possible in 2021. Akebia and its collaborator, Otsuka Pharmaceutical Co. Ltd., are working in close collaboration to prepare a Marketing Authorization Application (MAA) for submission to the European Medicines Agency (EMA).

"We remain confident that we have a path toward potential approval for vadadustat in dialysis supported by positive top-line results for efficacy and safety from $INNO_2$VATE. PRO_2TECT delivered positive top-line efficacy results; however, the MACE result presents challenges to achieving our goal of bringing vadadustat to patients in the non-dialysis market. While achieving the MACE endpoint would have made our path here more straightforward, as it is in dialysis, we still believe we have a path toward approval for vadadustat in non-dialysis," stated John P. Butler, President and Chief Executive Officer of Akebia Therapeutics. "We believe the cardiovascular safety of vadadustat is supported by the totality of the data from our global Phase 3 program, including additional analyses on cardiovascular outcomes observed within key geographic regions and across certain patient sub-populations within PRO_2TECT."

Butler continued, "With data in hand, we and Otsuka have already started working on vadadustat's NDA. At this time, we're planning for a pre-NDA meeting with the FDA before the end of the year, followed by our NDA filing for both the dialysis and non-dialysis indications as early as possible next year. Together with Otsuka, we believe we have an extensive data package to support the potential approval of vadadustat in both indications. We look forward to putting this package in front of health authorities as soon as possible and sharing the full dataset from our global Phase 3 program at an upcoming medical conference."

Global Phase 3 PRO_2TECT Program

Akebia's global PRO_2TECT program is a cardiovascular outcomes program that includes two separate Phase 3 studies (*Correction* and *Conversion*), which collectively enrolled 3,476 adult patients not on dialysis with anemia due to CKD. Both PRO_2TECT studies are global, multicenter, open label (sponsor blinded), active-controlled (darbepoetin alfa - an injectable erythropoiesis stimulating agent (ESA)), non-inferiority studies. In both studies, patients were randomized 1:1 to receive either vadadustat or darbepoetin alfa. Vadadustat was initiated at a starting oral dose of 300 mg once daily and adjusted over time in increments of 150 mg within the range of 150 to 600 mg daily using a dose adjustment algorithm, while darbepoetin alfa was dosed per the U.S. package insert (USPI) or summary of product characteristics (SmPCs) in appropriate geographies.

The PRO_2TECT *Correction* study evaluated 1,751 patients with anemia due to CKD without recent ESA use (879 and 872 patients randomized to vadadustat and darbepoetin alfa, respectively). The PRO_2TECT *Conversion* study evaluated 1,725 patients with anemia due to CKD on an active ESA treatment (862 and 863 patients randomized to vadadustat and darbepoetin alfa, respectively).

In both PRO_2TECT studies, the primary efficacy endpoint was the mean change in Hb between baseline and the primary evaluation period (weeks 24-36). Non-inferiority was achieved if the lower bound of the 95% confidence interval (CI) for the between-group difference of the mean Hb change did not fall below the pre-specified NI margin (-0.75 g/dL). The PRO_2TECT program's primary safety endpoint, MACE, was independently and blindly assessed by the Brigham and Women's Hospital's Clinical Endpoint Center (BWH CEC) in Boston, MA, with a comparison of vadadustat to darbepoetin alfa. MACE is defined as the composite endpoint of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke. To assess MACE, a combined analysis of time to first MACE event from the two PRO_2TECT studies was performed. NI was achieved if the upper bound of the 95% confidence interval for the hazard ratio of vadadustat to darbepoetin alfa did not exceed the pre-specified NI margin of 1.25.

Primary and Key Secondary Efficacy Endpoint Results
Vadadustat achieved each of the PRO_2TECT studies' primary efficacy endpoints of mean change in Hb between baseline and the primary evaluation period (mean Hb from weeks 24 to 36) compared to darbepoetin alfa, in adult patients on dialysis, demonstrating non-inferiority to darbepoetin alfa using an NI margin of -0.75 g/dL prospectively agreed to with FDA and EMA.

In PRO_2TECT's *Correction* study (n=1,751):

- **Primary Efficacy Endpoint Result**: Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was 0.05 g/dL (95% CI: -0.04, 0.15), achieving the pre-specified NI criterion of -0.75 g/dL. The mean (SD) Hb level at week 24 to week 36 was 10.39 (0.99) g/dL for vadadustat-treated patients compared to 10.35 (1.03) g/dL for darbepoetin alfa-treated patients.
- **Key Secondary Efficacy Endpoint Result**: Vadadustat sustained the target Hb efficacy response at weeks 40 to 52 achieving non-inferiority compared to darbepoetin alfa. The least square mean difference in Hb was 0.04 g/dL (95% CI: -0.06, 0.14). The mean (SD) Hb level at week 40 to week 52 was 10.48 (1.05) g/dL for vadadustat-treated patients compared to 10.45 (1.01) g/dL for darbepoetin alfa-treated patients.

In PRO_2TECT's *Conversion* study (n=1,725):

- **Primary Efficacy Endpoint Result**: Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was -0.01 g/dL (95% CI: -0.09, 0.07), achieving the pre-specified NI criterion of -0.75 g/dL. The mean (SD) Hb level at week 24 to week 36 was 10.77 (0.98) g/dL for vadadustat-treated patients compared to 10.77 (0.99) g/dL for darbepoetin alfa-treated patients.
- **Key Secondary Efficacy Endpoint Result**: Vadadustat sustained efficacy in the *Conversion* study demonstrating non-inferiority to darbepoetin with a least square mean difference in Hb of 0.00 g/dL (95% CI: -0.10, 0.09). The mean (SD) Hb level at week 40 to week 52 was 10.80 (1.04) g/dL in the vadadustat-treated patients compared to 10.79 (1.05) g/dL for darbepoetin alpha-treated patients.

Primary Safety MACE Endpoint Result
The PRO_2TECT program (*Correction* and *Conversion* studies) (n=3,471):

- **Primary Safety MACE Endpoint Result**: Vadadustat did not meet the PRO_2TECT program's primary safety endpoint of non-inferiority for MACE. The upper bound of the 95% confidence interval of the Hazard Ratio (HR) was above the pre-specified NI margin of 1.25 for primary MACE analysis (HR 1.17, 95% CI: 1.01, 1.36). MACE is defined as the composite endpoint of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke.

The incidence of treatment emergent adverse events during the *Correction* study in the vadadustat-treated patients was 90.9%, and 91.6% in darbepoetin alfa-treated patients. During the study, the most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa-treated patients were end-stage renal disease (34.7%/ 35.2%), hypertension (17.7%/ 22.1.%), hyperkalemia (12.3.%/ 15.6%), urinary tract infection (12.9%/ 12.0%), diarrhea (13.9%/ 10.0%), peripheral oedema (12.5%/ 10.5%), fall (9.6%/ 10%) and nausea (10%/ 8.2%). Serious treatment emergent adverse events were 65.3% for vadadustat-treated patients and 64.5% for darbepoetin alfa-treated patients. The incidence of treatment emergent adverse events during the *Conversion* study in vadadustat treated patients was 89.1% and 87.7% in darbepoetin alfa-treated patients. During the study, the most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa-treated patients were end-stage renal disease (27.5%/ 28.4%), hypertension (14.4%/ 14.8%), urinary tract infection (12.2%/ 14.5%), diarrhea (13.8.%/ 8.8.%), peripheral oedema (9.9%/ 10.1%) and pneumonia (10.0%/ 9.7%). Serious treatment emergent adverse events were 58.5% for vadadustat-treated patients and 56.6% for darbepoetin alfa-treated patients.

"The results of Akebia's global Phase 3 program continue to underscore the potential of vadadustat as a once-daily oral standard of care for patients living with anemia due to CKD, upon approval," stated Steven K. Burke, M.D., Senior Vice President, Research & Development and Chief Medical Officer of Akebia Therapeutics. "There is a significant unmet medical need among patients living with anemia due to CKD, and we are excited to be advancing vadadustat as a potential therapy for these patients. I would like to extend our sincere thanks to everyone involved in this study, including the patients, physicians, investigators and their staff."

Investor Conference Call and Live Webcast:
Akebia will host a conference call with accompanying slides today, Thursday, September 3, 2020, at 8:30 a.m. Eastern Time to discuss the

PRO$_2$TECT data. To listen to the conference call, please dial (877) 458-0977 (domestic) or (484) 653-6724 (international) using conference ID number 9547389. A live webcast of the call with accompanying slides can be accessed via the Investors section of the Company's website at https://ir.akebia.com/.

A replay of the conference call will be available two hours after the completion of the call through September 9, 2020. To access the replay, dial (855) 859-2056 (domestic) or (404) 537-3406 (international) and reference conference ID number 9547389. A replay of the webcast, and accompanying slides, can be accessed via the Investors section of the Company's website at https://ir.akebia.com/.

About Akebia Therapeutics
Akebia Therapeutics, Inc. is a fully integrated biopharmaceutical company with the purpose to better the lives of people impacted by kidney disease. The Company was founded in 2007 and is headquartered in Cambridge, Massachusetts. For more information, please visit our website at www.akebia.com, which does not form a part of this release.

About Vadadustat
Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor designed to mimic the physiologic effect of altitude on oxygen availability. At higher altitudes, the body responds to lower oxygen availability with stabilization of hypoxia-inducible factor, which can lead to increased red blood cell production and improved oxygen delivery to tissues. Vadadustat is in global Phase 3 development for the treatment of anemia due to CKD and is not approved by the U.S. Food and Drug Administration (FDA) or any regulatory authority with the exception of Japan's Ministry of Health, Labour and Welfare (MHLW). In Japan, vadadustat is approved as a treatment for anemia due to CKD in both dialysis-dependent and non-dialysis dependent adult patients.

About Anemia due to Chronic Kidney Disease (CKD)
Anemia is a condition in which a person lacks enough healthy red blood cells to carry adequate oxygen to the body's tissues. It commonly occurs in people with CKD because their kidneys do not produce enough erythropoietin (EPO), a hormone that helps regulate production of red blood cells. Anemia due to CKD can have a profound impact on a person's quality of life as it can cause fatigue, dizziness, shortness of breath and cognitive dysfunction. Left untreated, anemia leads to deterioration in health and is associated with increased morbidity and mortality in people with CKD.

Forward Looking Statements
Statements in this press release regarding Akebia's strategy, plans, prospects, expectations, beliefs, intentions and goals are forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, as amended, including but not limited to statements regarding Akebia's belief that the totality of the data from its global Phase 3 program for vadadustat supports the cardiovascular safety of vadadustat, an NDA submission and marketing approval in both the dialysis and non-dialysis indications; the path for approval of vadadustat in dialysis and non-dialysis; the potential challenges with respect to achieving an approval for vadadustat in the non-dialysis indication; the assessment of the data from PRO2TECT, including additional analyses on cardiovascular outcomes observed within key geographic regions and across certain patient sub-populations; the potential for marketing approval of vadadustat in dialysis and non-dialysis; the Company's goal of bringing vadadustat to patients in the dialysis and non-dialysis markets; the timing of meetings with regulators, including the pre-NDA meeting with the FDA; safety and efficacy of vadadustat; the potential indications for and benefits of vadadustat; sharing vadadustat clinical data, including the full dataset from INNO2VATE and PRO2TECT, at an upcoming medical conference, in peer reviewed journals and with health authorities and others, as well as the timing and forum thereof; submitting filings for marketing approval of vadadustat, and the timing thereof; the potential launch and commercialization of vadadustat if approved by regulatory authorities; and market opportunity, clinical opportunity, commercial potential, prevalence, and the growth in, and potential demand for, vadadustat. The terms "advance," "believe," "goal," "look forward," "opportunity," "planned," "potential," "will" and similar references are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement, including the timing and content of advice given and decisions made by health authorities, including marketing approval and labeling decisions; the actual time it takes to make regulatory submissions for vadadustat to health authorities, including the submission of the NDA to the FDA and the MAA to EMA; risks associated with the Priority Review Voucher for vadadustat; the potential direct or indirect impact of the COVID-19 pandemic on our business, operations, and the markets and communities in which we and our partners, collaborators, vendors and customers operate; manufacturing and quality risks; risks associated with management and key personnel changes and transitional periods; the actual funding required to continue to commercialize our commercial product, develop and commercialize vadadustat and operate the Company; market acceptance and coverage and reimbursement of our commercial product and vadadustat, if approved; the risks associated with potential generic entrants for our commercial product and vadadustat, if approved; early termination of any of Akebia's collaborations; Akebia's and its collaborators' ability to satisfy their obligations under Akebia's collaboration agreements; the competitive landscape for our commercial product and vadadustat; the scope, timing, and outcome of any legal, regulatory and administrative proceedings; changes in the economic and financial conditions of the businesses of Akebia and its partners; and Akebia's ability to obtain, maintain and enforce patent and other intellectual property protection for our commercial product, vadadustat and any other product candidates. Other risks and uncertainties include those identified under the heading "Risk Factors" in Akebia's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and other filings that Akebia may make with the U.S. Securities and Exchange Commission in the future. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Akebia does not undertake, and specifically disclaims, any obligation to update any forward-looking statements contained in this press release.

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