Akebia Therapeutics Announces Positive Top-Line Results from Global Phase 3 Program of Vadadustat for Treatment of Anemia Due to Chronic Kidney Disease in Adult Patients on Dialysis

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- Vadadustat achieved primary efficacy and cardiovascular safety endpoints
- Clear, consistent top-line data advances plan for vadadustat's New Drug Application and other global regulatory submissions
- Company to discuss top-line data on its scheduled first quarter financial results conference call today at 8:30 a.m. ET

CAMBRIDGE, Mass., May 5, 2020 /PRNewswire/ -- Akebia Therapeutics, Inc. (Nasdaq: AKBA), a biopharmaceutical company with the purpose to better the lives of people impacted by kidney disease, today announced positive top-line results from $INNO_2VATE$, the first of its two global Phase 3 cardiovascular outcomes programs. The two $INNO_2VATE$ 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 on dialysis.

Vadadustat achieved the primary and key secondary efficacy endpoint in each of the two $INNO_2VATE$ studies, demonstrating non-inferiority 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 also achieved the primary safety endpoint of the $INNO_2VATE$ 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, or non-fatal stroke across both $INNO_2VATE$ studies. Each analysis was measured against non-inferiority (NI) margins agreed upon with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

"The $INNO_2VATE$ study results are very compelling," stated Glenn Chertow, M.D., M.P.H., Professor of Medicine, Chief, Division of Nephrology at Stanford University, and Co-Chair of the independent Executive Steering Committee for $INNO_2VATE$. "The greatest strength of the $INNO_2VATE$ data is the consistency across both efficacy and all MACE components. The nephrology community has been eagerly awaiting straightforward, high-quality data evaluating the treatment of anemia due to CKD with a novel HIF-PHI. Based on these two randomized trials comparing vadadustat to the active darbepoetin control, I am confident that vadadustat has the potential to be a safe and effective option for the treatment of anemia due to CKD in adult patients requiring dialysis, upon approval."

John P. Butler, President and Chief Executive Officer of Akebia Therapeutics stated, "We are thrilled to be sharing positive top-line data from $INNO_2VATE$, the first of our two global Phase 3 programs studying vadadustat to treat anemia due to CKD. It is extremely rewarding to see this program yield clear, consistent, straightforward results. We believe our data uniquely positions vadadustat as a potential new oral standard of care for treating all populations of dialysis patients, including both incident and prevalent dialysis patients, with anemia due to CKD, subject to approval."

"We look forward to sharing these compelling data with regulators, as well as with physicians, dialysis providers and payers. We are more confident than ever that the clinical success we've demonstrated with $INNO_2VATE$ supports vadadustat's potential for regulatory and commercial success, upon approval." Butler continued, "The team is already at work on vadadustat's New Drug Application (NDA), which we expect to file as quickly as possible following the top-line data readout of PRO_2TECT, our global Phase 3 program studying vadadustat in adult patients not on dialysis with anemia due to CKD, which we expect in mid-2020, as planned. We believe that the $INNO_2VATE$ data will be highly informative for physicians, patients, dialysis providers and payers, as they make important decisions about patient care, once vadadustat is approved."

Global Phase 3 $INNO_2VATE$ Program

Akebia's global $INNO_2VATE$ program is a cardiovascular outcomes program that includes two separate Phase 3 studies (*Correction/Conversion* and *Conversion*), which collectively enrolled 3,923 adult patients on dialysis with anemia due to CKD. Both $INNO_2VATE$ 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 US package insert (USPI) or summary of product characteristics (SmPCs) in appropriate geographies.

The $INNO_2VATE$ *Correction/Conversion* study evaluated 369 incident dialysis patients (181 and 188 patients randomized to vadadustat and darbepoetin alfa, respectively) who initiated chronic dialysis (either peritoneal dialysis (PD) or hemodialysis (HD)) for end-stage renal disease (ESRD) ≤ 16 weeks prior to screening and had limited exposure to recombinant erythropoiesis stimulating agents (rESAs). The $INNO_2VATE$ *Conversion* study evaluated 3,554 dialysis patients (1,777 and 1,777 patients randomized to vadadustat and darbepoetin alfa, respectively) currently receiving rESA who were converted to either vadadustat or darbepoetin alfa.

In both $INNO_2VATE$ studies, the primary efficacy endpoint was the mean change in Hb between baseline and the primary evaluation period (weeks 24-36). NI was achieved if the lower bound of the 95% confidence interval for the between-group difference of the mean Hb change did not fall below the pre-specified NI margin (-0.75 g/dL). The $INNO_2VATE$ 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, or non-fatal stroke. To assess MACE, a combined analysis of time to first MACE event from the two INNO$_2$VATE 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 INNO$_2$VATE 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 based on using a non-inferiority margin of -0.75 g/dL prospectively agreed to with FDA and EMA.

In INNO$_2$VATE's *Correction/Conversion* study of incident dialysis patients (n=369):

- **Primary Efficacy Endpoint Result**: Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was -0.31 g/dL (95% CI: -0.53, -0.10), achieving the pre-specified non-inferiority criterion of -0.75 g/dL. The mean (SD) Hb level at week 24 to week 36 was 10.36 (1.13) g/dL for vadadustat-treated patients compared to 10.61 (0.94) 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 -0.07 g/dL (95% CI: -0.34, 0.19). The mean (SD) Hb level at week 40 to week 52 was 10.51 (1.19) g/dL for vadadustat treated-patients compared to 10.55 (1.14) g/dL for darbepoetin alfa-treated patients.

In INNO$_2$VATE's *Conversion* study of dialysis patients (n=3,554):

- **Primary Efficacy Endpoint Result**: Vadadustat was non-inferior to darbepoetin alfa. The least square mean difference in Hb was -0.17 g/dL (95% CI: -0.23, -0.10), achieving the pre-specified non-inferiority criterion of -0.75 g/dL. The mean (SD) Hb level at week 24 to week 36 was 10.36 (1.01) g/dL for vadadustat-treated patients compared to 10.53 (0.96) 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 -0.18 g/dL (95% CI: -0.25, -0.12). The mean (SD) Hb level at week 40 to week 52 was 10.40 (1.04) g/dL in the vadadustat-treated patients compared to 10.58 (0.98) g/dL for darbepoetin treated patients.

Primary Safety Major Adverse Cardiovascular Events (MACE) Endpoint Result
Vadadustat achieved the INNO$_2$VATE program's primary safety endpoint of non-inferiority for MACE. In the primary analysis of time to first MACE event, vadadustat demonstrated non-inferiority to darbepoetin alfa using a non-inferiority margin of 1.25 prospectively agreed to by FDA and a non-inferiority margin of 1.3 prospectively agreed to by EMA.

The INNO$_2$VATE program (*Correction/Conversion* and *Conversion* studies) of dialysis patients (n=3,902):

- Vadadustat was non-inferior to darbepoetin alfa. The upper bound of the 95% confidence interval (CI) of the Hazard Ratio (HR) was below the pre-specified non-inferiority margin of 1.25 for primary MACE analysis. (HR 0.96, 95% CI: 0.83, 1.11.) MACE is defined as the composite endpoint of all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke.

The incidence of treatment emergent adverse events during the *Correction/Conversion* study in vadadustat treated patients was 83.8% and 85.5% in darbepoetin alfa treated patients. During the study, the most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa treated patients were hypertension (16.2%/ 12.9%) and diarrhea (10.1%/ 9.7%). Serious treatment emergent adverse events were lower in vadadustat treated patients at 49.7% compared to 56.5% for darbepoetin alfa treated patients. The incidence of treatment emergent adverse events during the *Conversion* study in the vadadustat treated patients was 88.3%, and 89.3% in darbepoetin alfa treated patients. During the study, the most common treatment emergent adverse events reported in vadadustat/darbepoetin alfa treated patients were diarrhea (13.0%/ 10.1%), pneumonia (11.0%/ 9.7%), hypertension (10.6%/ 13.8%), and hyperkalemia (9.0%/ 10.8%). Serious treatment emergent adverse events were slightly lower for vadadustat treated patients at 55.0% and 58.3% for darbepoetin alfa-treated patients.

"With nearly 4,000 patients participating in INNO$_2$VATE and a total exposure of just over 2,200 patient-years with vadadustat, INNO$_2$VATE has been a tremendous undertaking. We would like to extend our sincere thanks to everyone involved in this study including the patients, physicians, investigators and site coordinators," said Steven K. Burke, M.D., Senior Vice President, Research & Development and Chief Medical Officer of Akebia. "We believe vadadustat has the potential to play a key role in the treatment of anemia due to CKD, and we are another step closer to realizing that vision. We are very pleased with these clear and consistent findings and are excited to share the full data set, together with the data from our PRO$_2$TECT studies, later this year at a medical conference and in a peer-reviewed journal."

Upon successful completion of the Phase 3 program, which includes the PRO$_2$TECT studies of vadadustat for the treatment of anemia due to CKD in adult patients not on dialysis that the Company expects to read out mid-2020, Akebia plans to submit to FDA an NDA for vadadustat for the treatment of anemia due to CKD in adult dialysis-dependent and non-dialysis dependent patients. In close coordination with its collaborator, Otsuka Pharmaceutical Co. Ltd., the Company also plans to submit a Marketing Authorization Application (MAA) to EMA. Akebia and Otsuka are collaborating on the development and commercialization of vadadustat in the US, Europe, China, Russia, Canada, Australia, the Middle East, and certain other territories. A Japanese New Drug Application (JNDA) for vadadustat was submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) in July 2019 by Mitsubishi Tanabe Pharma Corporation (MTPC), Akebia's development and commercialization collaboration partner in Japan for vadadustat.

Conference Call:
Akebia will host a conference call with slides today, Tuesday, May 5, 2020, at 8:30 a.m. Eastern Time to discuss its INNO$_2$VATE data and its first quarter financial results. To listen to the conference call, please dial (877) 458-0977 (domestic) or (484) 653-6724 (international) using conference ID number 8464788. The call will also be webcast LIVE with slides and can be accessed via the Investors section of the Company's website at https://ir.akebia.com/

A replay of the conference call and the slides will be available two hours after the completion of the call through May 11, 2020. To access the replay, dial (855) 859-2056 (domestic) or (404) 537-3406 (international) and reference conference ID number 8464788. An online archive of the conference call 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 currently in global Phase 3 development for the treatment of anemia due to CKD. Vadadustat is 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 an investigational therapy and is not approved by the U.S. Food and Drug Administration (FDA) or any regulatory authority.

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 the assessment of the data from INNO$_2$VATE; safety and efficacy of vadadustat; the potential indications for and benefits of vadadustat; vadadustat clinical trial data and results and the anticipated timing of the availability and reporting thereof; sharing vadadustat clinical data, including the full data set from INNO$_2$VATE and PRO$_2$TECT, with regulators 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 size, commercial potential, prevalence, and the growth in, and potential demand for, vadadustat. The terms "anticipate," "believe," "expect," "opportunity," "planned," "potential," "target," "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 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; the risk that existing preclinical and clinical data may not be predictive of the results of ongoing or later clinical trials, including PRO$_2$TECT; the risk that clinical trials may not be successful; manufacturing risks; risks associated with the Priority Review Voucher for vadadustat; risks associated with management and key personnel changes and transitional periods; the actual funding required to develop and commercialize our commercial product, vadadustat and other product candidates and operate the Company, and the actual expenses associated therewith; the actual costs incurred in the clinical studies of vadadustat and the availability of financing to cover such costs; the risk that clinical studies are discontinued or delayed for any reason, including for safety, tolerability, enrollment, manufacturing or economic reasons; 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 timing and content of decisions made by regulatory authorities; the timing of any additional studies initiated for vadadustat; the actual time it takes to initiate and complete preclinical and clinical studies; 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 Annual Report on Form 10-K for the year ended December 31, 2019 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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