Acumen Pharmaceuticals Presents Late-Breaker Phase 1 Updates Exploring Novel Target Engagement, Dosing Regimen and Safety Findings for ACU193 in Early Alzheimer's Disease at the 16th Annual Clinical Trials on Alzheimer's Disease

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- Acumen presented data exploring target engagement modeling of ACU193, the first clinical-stage amyloid beta oligomer (AβO)-targeting antibody, to inform dose selection, plus further analyses of dose-related amyloid plaque reduction and clinical characteristics of ARIA-E, confirming proof-of-mechanism for ACU193

- Announced dose selection of 50 mg/kg and 35 mg/kg every 4 weeks for ACU193 treatment arms in upcoming Phase 2/3 trial based on significant target engagement approaching maximal effect

- New data from additional exploratory analyses of ACU193 presented in four additional poster presentations discussing clinical trial recruitment and diversity, pharmacokinetics and target engagement assay characteristics

CHARLOTTESVILLE, Va. and INDIANAPOLIS, Ind., Oct. 27, 2023 (GLOBE NEWSWIRE) -- Acumen Pharmaceuticals, Inc. (NASDAQ: ABOS), a clinical-stage biopharmaceutical company developing a novel therapeutic that targets toxic soluble amyloid beta oligomers (AβOs) for the treatment of Alzheimer's disease (AD), today presented further analyses of the Phase 1 INTERCEPT-AD trial evaluating ACU193, the first clinical-stage AβO-targeting antibody, at the 16th Annual Clinical Trials on Alzheimer's Disease (CTAD) conference in Boston and online. The additional analyses reveal robust target engagement data modeling informing dose selection for Acumen's upcoming Phase 2/3 trial, as well as further details and characteristics around the observed plaque reduction and relatively low overall levels of ARIA-E during a late breaking symposium. Acumen additionally presented new target engagement and pharmacokinetic (PK) analyses from clinical trial recruitment in four posters at the conference.

Acumen plans to progress to a Phase 2/3 clinical study, with the Phase 2 portion planned to begin in the first half of 2024.

Positive topline results from the Phase 1 INTERCEPT-AD, announced in July 2023, demonstrated that ACU193 was well-tolerated with a compelling overall safety profile, meeting the primary objective of this Phase 1 study in both single- and multiple-dose regimens in 62 participants with early AD. Results also demonstrated dose related plaque reduction, low overall ARIA-E and PK results supporting dosing of ACU193 every four weeks (Q4W), ultimately confirming proof-of-mechanism for the first clinical-stage monoclonal antibody designed to selectively bind AβOs while potentially offering improved safety and clinical benefit over existing amyloid-directed therapies. Further analyses and data modeling of the robust Phase 1 dataset, presented at CTAD, shed deeper insights into the broad therapeutic potential of ACU193 and the clinical validity of targeting AβOs, while helping to inform the subsequent Phase 2/3 study that will assess clinical efficacy.

"We are pleased to present new analyses from the INTERCEPT-AD trial that expand our understanding of the pharmacokinetics and pharmacodynamics of ACU193, as well as announce the dose levels selected for our next clinical study," said Daniel O'Connell, President and Chief Executive Officer of Acumen. "The robust Phase 1 dataset not only validate our confidence in ACU193 as a differentiated amyloid-directed therapy with a novel target, but also offer crucial insights that have helped shape the next phase of study, during which we look forward to evaluating ACU193 in early AD patients over a longer-term period to assess clinical efficacy. I'd like to thank everyone involved in INTERCEPT-AD – especially the participants and their families – for the invaluable contributions they made to this remarkably extensive study."

In a late-breaking symposium, titled "INTERCEPT-AD phase 1 insights and findings from the investigation of ACU193, a monoclonal antibody targeting soluble Aβ oligomers," detailed results were discussed during the following presentations:

Determination of Target Engagement at Various Doses of ACU193 in INTERCEPT-AD
ACU193 demonstrated direct target engagement of toxic AβOs in a dose-proportional manner, using a novel assay to measure cerebral spinal fluid (CSF) concentrations of ACU193 bound to AβOs, which approached maximal target engagement (Emax) with higher doses of ACU193 (60mg/kg). Further analysis of this novel endpoint, based on robust pharmacokinetic/pharmacodynamic data modeling conducted in collaboration with Certara, demonstrated the pharmacokinetics of ACU193 in CSF and its correlation with dose and dose regimen and serum PK (based on measurable exposures of post-dose ACU193 concentration in CSF for both single- and multiple-dose regimens). Modeling the target engagement Emax curve offered the opportunity to select doses of 35 and 50 mg/kg with substantial target engagement of AβOs for the Phase 2/3 study. Amyloid plaque reduction results from the Phase 1 trial were also considered in the selection of 35 and 50 mg/kg doses, which will be evaluated versus placebo in the Phase 2/3 study.

Reduction in Amyloid Plaque Load at Higher Doses of ACU193 in INTERCEPT-AD (with relatively low levels of ARIA-E)
In INTERCEPT-AD, dose-related, statistically significant amyloid plaque reduction that was comparable to approved and in-review therapies at similar time points, was observed in higher dose cohorts (60 mg/kg Q4W and 25 mg/kg Q2W). This finding demonstrates ACU193's activity in the brain and is a positive development given the relationship between robust plaque reduction and slowing clinical decline established by other Aβ-targeting antibodies. The amyloid positron emission tomography (PET) data for inclusion in the study were assessed using a hybrid approach to evaluating amyloid positivity in PET scans based on SUVr and, in some cases, visual reads, which may be useful in detecting amyloid positivity below the SUVr threshold. These visual reads may be of particular importance for patients with early AD. The presentation also explored potential mechanistic explanations for the unexpected plaque reduction effect of ACU193 with limited ARIA-E, given its selectivity for AβOs and minimal binding of other Aβ species. A Phase 2/3 study is planned to assess primarily the clinical efficacy of ACU193 and also to more fully understand its effect on plaques.

Characteristics of Participants in INTERCEPT-AD Who Did or Did Not Develop ARIA with ACU193
As previously reported, the INTERCEPT-AD study demonstrated overall low incidence of ARIA-E, with five cases of ARIA-E in the 48 participants treated with ACU193. In further subgroup data, as presented by Dr. Stephen Salloway, M.D., M.S., Alpert Medical School of Brown University, four of

the five cases of ARIA-E occurred in APOE4 heterozygotes and none in APOE4 homozygotes. The presentation also detailed characteristics among participants who did and did not experience amyloid plaque reduction, helping to shed light on possible explanations for the variability in the reduction of plaque load seen in different participants.

“Following ACU193’s significant target engagement of AβOs, as determined by our novel assay designed to detect this difficult-to-quantify species of Aβ, I am pleased with the data modeling of the exposure-response relationship, or Emax curve, for target engagement that allowed us to select the two doses for the next phase of study,” said Eric Siemers, M.D., Chief Medical Officer of Acumen. “Our Phase 1 study design generated a range of clear outcomes that go beyond typical Phase 1 trials and are crucial to expanding our understanding of the broad therapeutic potential of ACU193.”

In addition to the symposium topics, Acumen presented four posters describing the baseline characteristics for INTERCEPT-AD participants as well as study recruitment techniques that were used to help Acumen recruit a diverse population for the trial.

INTERCEPT-AD: ACU193 CSF pharmacokinetics in early Alzheimer’s disease
As previously presented, ACU193 pharmacokinetics in the CSF was characterized by dose-proportional exposure in both the single- and multiple-dose cohorts, suggestive of ACU193’s intended drug effect in the central nervous system (CNS). An ultra-sensitive assay developed to assess ACU193 drug concentration in the CNS of study participants confirmed that a decrease in ACU193 concentration in the CSF since last dose demonstrated drug clearance from the CNS over time.

Development of Novel Bioanalytical Assays: ACU193-sAβO Complex Measurement in CSF: Additional Analyses Using a Sensitive Assay of Target Engagement for the sAβO-Selective Antibody ACU193 in INTERCEPT-AD
Using the first target engagement assay specific for an AβO-targeting antibody, INTERCEPT-AD evaluated the ability of ACU193 to engage its intended AβO target in the CNS, with the initial analysis revealing dose-dependent target engagement for ACU193 that approached maximal engagement at the highest doses. Additional analyses with a sensitive assay of the target engagement data showed that ACU193 bound to AβO (or ACU193-AβO complex) in the CSF was present in ACU193-treated participants only (as opposed to those with placebo). In comparison of post-dose samples, ACU193-AβO complex levels decreased over time from the last dose, with the highest complex levels measured within 11 days of dosing.

Additional poster presentations explored patient recruitment strategies and eligibility considerations that influenced the diversity of INTERCEPT-AD participants, as well as a review of participant exit survey responses related to the trial experience that will help to inform operational aspects of subsequent trial phases.

The full results of the INTERCEPT-AD study will be presented at a future medical congress and submitted for publication in a peer-reviewed clinical journal. Fluid biomarker data are expected by the end of this year.

About ACU193

ACU193 is a humanized monoclonal antibody (mAb) discovered and developed based on its selectivity for soluble AβOs, which Acumen believes are the most toxic and pathogenic form of Aβ, relative to Aβ monomers and amyloid plaques. Soluble AβOs have been observed to be potent neurotoxins that bind to neurons, inhibit synaptic function and induce neurodegeneration. By selectively targeting toxic soluble AβOs, ACU193 aims to directly address a growing body of evidence indicating that soluble AβOs are a primary underlying cause of the neurodegenerative process in Alzheimer’s disease. ACU193 has been granted Fast Track designation for the treatment of early Alzheimer’s disease by the U.S. Food and Drug Administration.

About INTERCEPT-AD

INTERCEPT-AD is a Phase 1, U.S.-based, multi-center, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and tolerability, and establishing clinical proof of mechanism, of ACU193 in patients with early Alzheimer’s disease (AD). Sixty-five individuals with early AD (mild cognitive impairment or mild dementia due to AD) enrolled in this first-in-human study of ACU193. The INTERCEPT-AD study consists of single-ascending-dose (SAD) and multiple-ascending-dose (MAD) cohorts and is designed to evaluate the safety, tolerability, pharmacokinetics (PK), and target engagement of intravenous doses of ACU193. More information can be found on www.clinicaltrials.gov, NCT identifier NCT04931459.

About Acumen Pharmaceuticals, Inc.

Acumen, headquartered in Charlottesville, VA, with clinical operations based in Carmel, IN, is a clinical-stage biopharmaceutical company developing a novel therapeutic that targets toxic soluble amyloid beta oligomers (AβOs) for the treatment of Alzheimer’s disease (AD). Acumen’s scientific founders pioneered research on AβOs, which a growing body of evidence indicates are early and persistent triggers of Alzheimer’s disease pathology. Acumen is currently focused on advancing its investigational product candidate, ACU193, a humanized monoclonal antibody that selectively targets toxic soluble AβOs. For more information, visit www.acumenpharm.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Words such as “believes,” “expects,” “anticipates,” “aims,” “plans,” “potential,” “will,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements include statements concerning the safety profile and mechanism of action of Acumen’s product candidate, ACU193, the regulatory path and clinical development of ACU193, including a possible Phase 2/3 study, and the timing of the presentation of additional data on ACU193. These statements are based upon the current beliefs and expectations of Acumen management, and are subject to certain factors, risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing safe and effective human therapeutics. Such risks may be amplified by the impacts of geopolitical events and macroeconomic conditions, such as rising inflation and interest rates, supply disruptions and uncertainty of credit and financial markets. These and other risks concerning Acumen’s programs are described in additional detail in Acumen’s filings with the Securities and Exchange Commission (“SEC”), including in Acumen’s most recent Annual Report on Form 10-K, and in subsequent filings with the SEC, including Acumen’s most recent Quarterly Report on Form 10-Q. Copies of these and other documents are available from Acumen. Additional information will be made available in other filings that Acumen makes from time to time with the SEC. These forward-looking statements speak only as of the date hereof, and Acumen expressly disclaims any obligation to update or revise any forward-looking statement, except as otherwise required by law, whether, as a result of new information, future events or otherwise.

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