Arvinas Presents First-in-Human Data for Investigational Oral PROTAC ARV-102 Demonstrating Blood-Brain Barrier Penetration, and Central and Peripheral LRRK2 Degradation

April 4, 2025

– Data demonstrate that ARV-102 was well tolerated, orally bioavailable, and brain-penetrant; ARV-102 achieved central and peripheral LRRK2 reduction indicating substantial LRRK2 protein degradation in healthy volunteers –

– Findings support continued evaluation of ARV-102 in neurodegenerative diseases associated with LRRK2 dysfunction; a Phase 1 trial in patients with Parkinson's disease has been initiated and is currently enrolling –

NEW HAVEN, Conn., April 04, 2025 (GLOBE NEWSWIRE) -- Arvinas, Inc. (Nasdaq: ARVN), a clinical-stage biotechnology company working to develop a new class of drugs based on targeted protein degradation, today presented data from the first-in-human clinical trial of ARV-102, the Company's investigational PROteolysis TArgeting Chimera (PROTAC) leucine-rich repeat kinase 2 (LRRK2) degrader. In the trial, ARV-102 demonstrated substantial reduction of LRRK2, a multifunctional protein that has been implicated in Parkinson's disease (PD) and progressive supranuclear palsy (PSP), in cerebral spinal fluid (CSF), with a promising safety/tolerability profile and favorable pharmacodynamic outcomes. Results from the randomized, double-blind, placebo-controlled single ascending dose (SAD) cohort of the Phase 1 healthy volunteer trial, and initial results from the multiple ascending dose (MAD) cohort, were shared in a presentation at the 2025 International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™ 2025) in Vienna, Austria.

The SAD cohort evaluated ARV-102 doses ranging from 10 mg to 200 mg. The MAD cohort evaluated doses ranging from 10 mg to 80 mg. Key findings from the trial showed:

- ARV-102 was generally safe and well tolerated with no serious adverse events reported after single or multiple doses.
- ARV-102 exposure in the CSF increased in a dose-dependent manner after single and multiple doses, indicating brain penetration.
- At a single oral dose of at least 60 mg, and once daily repeated oral doses of at least 20 mg, ARV-102 achieved greater than 50% LRRK2 reduction in the CSF and greater than 90% LRRK2 reduction in the peripheral blood mononuclear cells (PBMCs), indicating substantial central and peripheral LRRK2 protein degradation.
- Inhibition of Rab10 phosphorylation in PBMCs and reduction of bis(monoacylglycerol)phosphate (BMP) in urine following single doses of ARV-102, signifying downstream LRRK2 pathway engagement.

ARV-102 is a novel investigational oral PROTAC designed to cross the blood-brain barrier and target LRRK2. While LRRK2 is primarily known for its role in PD, emerging evidence suggests that it also plays a role in tauopathies, including PSP, and that LRRK2 dysfunction may contribute to the development and progression of both diseases.

"The ability of ARV-102 to cross the blood-brain barrier and degrade the LRRK2 protein offers a potentially transformative therapeutic approach in the treatment of devastating neurodegenerative diseases," said Noah Berkowitz, M.D., Ph.D., Chief Medical Officer at Arvinas. "We believe these results support continuing our ARV-102 clinical program and building upon our body of evidence for this lead PROTAC degrader candidate in our neuroscience pipeline."

Data presented at AD/PD™ 2025

The ARV-102 Phase 1 study is designed to assess the safety, pharmacokinetics, and pharmacodynamics of orally administered ARV-102 in healthy male volunteers. This is a single-center, randomized, double-blind, placebo-controlled trial evaluating outcomes in both SAD and MAD cohorts. In the SAD cohort, volunteers were randomized 3:1 to either placebo or a single dose of ARV-102 (10 mg, 30 mg, 60 mg, 90 mg, 150 mg, or 200 mg) on day 1 with follow-up until day 10. In the MAD cohort, volunteers were randomized to either placebo or a once daily dose of ARV-102 (10 mg, 20 mg, 40 mg, or 80 mg) for 14 days with follow-up until day 28.

Safety Profile

- At the time of data cutoff (March 13, 2025), the SAD cohort of the Phase 1 clinical trial is completed and the MAD cohort is ongoing. Based on evaluation of the available data from single and multiple oral doses, ARV-102 was well tolerated in healthy volunteers.
- Of the 47 volunteers across all SAD dose levels, the primary treatment related adverse events were headache and fatigue. Headaches occurred in 17.1% (6/35) of treated individuals compared to 0% (0/12) in placebo controls. Fatigue occurred in 8.6% (3/35) of the treated individuals compared to 25% (3/12) in placebo controls.
- Procedural pain associated with the lumbar puncture occurred in 28.6% (10/35) of treated individuals compared to 41.7% (5/12) in placebo controls. Post lumbar puncture syndrome was only observed in the treated cohort, at a rate of 17.1%

(6/35).
- No serious adverse events were reported in either the SAD or MAD cohorts.

ARV-102 Exposure in Plasma and CSF

- ARV-102 exhibited median maximum concentration (T_{max}) 6 hours after oral administration.
- The area under the concentration-time curve in the first 24 hours post dosing (AUC_{0-24}) and the maximum plasma concentration (C_{max}) increased in a dose-dependent manner and the median terminal plasma half-life ($t_{1/2}$) was 73 hours.
- ARV-102 levels in CSF increased in a dose dependent manner in both the SAD and MAD cohorts.

Pharmacodynamic Evaluation

- At single doses of greater than or equal to 60 mg and repeated doses of greater than or equal to 20 mg, LRRK2 reduction of greater than 90% in PBMCs was observed.
- ARV-102 at single doses of greater than or equal to 30 mg induced greater than 50% decreases in peripheral phospho-Rab10^{T73}, a LRRK2 substrate and biomarker for downstream LRRK2 activity; data for this endpoint in the MAD cohort is pending.
- ARV-102 at single doses of greater than or equal to 30 mg resulted in greater than 90% decrease of BMP in urine, a biomarker of lysosomal function; data for this endpoint in the MAD cohort is pending.
- In CSF, ARV-102 induced dose-dependent LRRK2 reduction, with greater than 50% LRRK2 reduction at single doses of greater than or equal to 60 mg and repeated doses of greater than or equal to 20 mg.

Arvinas believes these results support continued investigation of ARV-102 in neurodegenerative diseases associated with LRRK2 and lysosome dysfunction.

- In the fourth quarter of 2024, Arvinas initiated dosing in the SAD cohort of the Phase 1 clinical trial with ARV-102 in patients with PD (EUCT 2024-516888-84-00). The Company expects to complete enrollment and present initial data from the ongoing SAD cohort of the Phase 1 clinical trial in patients with PD and initiate the MAD cohort of the Phase 1 clinical trial in patients with PD, in 2025.

Additional detail on the ARV-102 data presentation at AD/PD 2025 follows below:

Session Title: First-In-Human Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of ARV-102, a PROTAC LRRK2 Degrader, in Healthy Males (ID:1963)

Session Type: Symposium: LRRK2, Alpha-Synuclein, Parkin: Diagnosis and Therapeutic Targets (ID:83)

Date: Friday, April 4, 2025

Lecture Time: 3:20 p.m. - 3:35 p.m. CET

About ARV-102

ARV-102 is an oral, brain-penetrant investigational PROTAC designed to degrade leucine-rich repeat kinase 2 (LRRK2), which is a large, multidomain scaffolding kinase. Increased activity and expression of LRRK2 have been implicated in the pathogenesis of neurological diseases, including LRRK2 genetic and idiopathic Parkinson's disease and progressive supranuclear palsy.

About Arvinas

Arvinas (Nasdaq: ARVN) is a clinical-stage biotechnology company dedicated to improving the lives of patients suffering from debilitating and life-threatening diseases. Through its PROTAC (PROteolysis TArgeting Chimera) protein degrader platform, the Company is pioneering the development of protein degradation therapies designed to harness the body's natural protein disposal system to selectively and efficiently degrade and remove disease-causing proteins. Arvinas is currently progressing multiple investigational drugs through clinical development programs, including vepdegestrant, targeting the estrogen receptor for patients with locally advanced or metastatic ER+/HER2- breast cancer; ARV-393, targeting BCL6 for relapsed/refractory non-Hodgkin Lymphoma; and ARV-102, targeting LRRK2 for neurodegenerative disorders. Arvinas is headquartered in New Haven, Connecticut. For more information about Arvinas, visit www.arvinas.com and connect on LinkedIn and X.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the potential for Arvinas' investigational oral PROteolysis TArgeting Chimera (PROTAC) degrader ARV-102 to treat neurodegenerative diseases associated with leucine-rich repeat kinase 2 (LRRK2) dysfunction; the ability of ARV-102 to cross the blood-brain barrier and degrade the LRRK2 protein offering a potentially transformative therapeutic approach in the treatment of neurodegenerative diseases; the first-in-human data for ARV-102 supporting continuing the ARV-102 clinical program and building upon Arvinas' body of evidence for ARV-102 in its neuroscience pipeline; LRRK2 dysfunction contributing to the development and progression of Parkinson's disease ("PD") and progressive supranuclear palsy ("PSP"); and Arvinas' plans relating to the completion of enrollment and presentation of initial data

from the ongoing single ascending dose cohort of the Phase 1 clinical trial of ARV-102 in patients with PD, and initiation of the multiple ascending dose cohort of the Phase 1 clinical trial of ARV-102 in patients with PD, including timings thereof. All statements, other than statements of historical facts, contained in this press release, including statements regarding Arvinas' strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Arvinas may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on such forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements Arvinas makes as a result of various risks and uncertainties, including but not limited to: whether Arvinas will be able to successfully conduct and complete development for its product candidates, including ARV-102, including whether Arvinas initiates and completes clinical trials for its product candidates and receives results from its clinical trials on its expected timelines or at all; Arvinas' ability to protect its intellectual property portfolio; whether Arvinas' cash and cash equivalent resources will be sufficient to fund its foreseeable and unforeseeable operating expenses and capital expenditure requirements; and other important factors discussed in the "Risk Factors" section of Arvinas' Annual Report on Form 10-K for the year ended December 31, 2024 and subsequent other reports on file with the U.S. Securities and Exchange Commission. The forward-looking statements contained in this press release reflect Arvinas' current views with respect to future events, and Arvinas assumes no obligation to update any forward-looking statements, except as required by applicable law. These forward-looking statements should not be relied upon as representing Arvinas' views as of any date subsequent to the date of this release.

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