ZyVersa Therapeutics Highlights Data Demonstrating Inflammasome Inhibition Reduces Neuroinflammation and Pathological Brain Deposition of Amyloid Beta in Alzheimer's Disease Mouse Model

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- Alzheimer's disease (AD), affecting around 6.9 million people in the US, is ranked as the seventh leading cause of death and is the most common cause of dementia among older adults.
- AD begins with buildup of amyloid beta (Aβ) plaques and neurofibrillary tangles in the brain that causes brain cells to die over time and the brain to shrink.
- The data demonstrate that initial deposition of Aβ triggers NLRP3 inflammasome activation causing release of ASC specks which rapidly enhance aggregation of Aβ. Aβ aggregates also activate NLRP3 inflammasomes thus triggering an ongoing cycle of IL-1β and ASC-mediated inflammation and Aβ deposition in the brain leading to AD progression. NLRP3 Inflammasome inhibition protected against development of AD pathology and neuroinflammation.
- These data support the potential of ZyVersa's Inflammasome ASC Inhibitor IC 100 as an effective treatment option for patients with neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. By targeting ASC, IC 100 inhibits activation of multiple inflammasome pathways including NLRP3. Likewise, IC 100 disrupts the function of ASC specks which enhance pathological aggregation of Aβ and perpetuate the inflammatory response.

WESTON, Fla., March 12, 2025 (GLOBE NEWSWIRE) -- ZyVersa Therapeutics, Inc. (Nasdaq: ZVSA, or "ZyVersa"), a clinical stage specialty biopharmaceutical company developing first-in-class drugs for treatment of inflammatory and renal diseases, highlights newly published data demonstrating that NLRP3 Inhibition attenuates development of AD pathology (buildup of Aβ) and neuroinflammation in a mouse model of AD, thereby attenuating disease progression.

"These data strengthen support for the potential role for Inflammasome ASC Inhibitor as a treatment for Alzheimer's and other neurological diseases, such as Parkinson's disease," said Stephen C. Glover, ZyVersa's Co-founder, Chairman, CEO and President. "Data from our preclinical program demonstrate that IC 100 decreased inflammasome activation and ASC speck formation in the cortex of aging mice. A second study in postmortem brains of people with Alzheimer's disease confirms that ASC expression correlates with Aβ and pTau in neurons. Labeled IC 100 associated with ASC in neurons in early stages of the disease thus offering potential as an imaging biomarker as well as a therapeutic option. Stay tuned for publication of data assessing the potential of IC 100 to block the damaging neuroinflammation that induces neural degeneration in Parkinson's disease, which has been submitted to a peer reviewed journal and is currently under review."

The new study data were published in the peer-reviewed journal, *Immunity*. In the publication titled, NLRP3-mediated glutaminolysis controls microglial phagocytosis to promote Alzheimer's disease progression , the researchers report data from studies conducted in a mouse model of Alzheimer's disease, murine microglia, and human THP-1 cells.

Key Findings

- Initial Aβ deposition directly triggers NLRP3 activation and neuroinflammation in AD mouse model, which was attenuated by NLRP3 inhibition.
- NLRP3 inhibition significantly increased degradation and elimination of Aβ in microglia via a process called phagocytosis.
- Increased microglia phagocytosis with NLRP3 inhibition was attributed to increased microglial metabolic activity: (1) NLRP3 inhibition increased glutamine utilization and α-ketoglutarate (αKG) levels; (2) αKG triggered phagocytic gene transcription, and this cellular reprogramming enhanced uptake and degradation of Aβ by microglia
- Data demonstrate an additional role for NLRP3 inhibition. In addition to attenuating damaging neuroinflammation, NLRP3 Inhibition increased mitochondrial and metabolic function, leading increased degradation and elimination of Aβ in microglia to attenuate progression of AD.

The authors concluded, "Our data strengthen NLRP3 as a master-immune regulator and an important target in the treatment of AD and dementia, both through its control on previously described inflammatory pathway and via the (metabolic) mechanism we describe here, bringing hope to the development of improved therapies for patients with this devastating condition."

About Inflammasome ASC Inhibitor IC 100

IC 100 is a novel humanized IgG4 monoclonal antibody that inhibits the inflammasome adaptor protein ASC. IC 100 was designed to attenuate both initiation and perpetuation of the inflammatory response. It does so by binding to a specific region of the ASC component of multiple types of

inflammasomes, including NLRP1, NLRP2, NLRP3, NLRC4, AIM2, and Pyrin. Intracellularly, IC 100 binds to ASC monomers, inhibiting inflammasome formation, thereby blocking activation of IL-1β early in the inflammatory cascade. IC 100 also binds to ASC in ASC Specks, both intracellularly and extracellularly, further blocking activation of IL-1β and the perpetuation of the inflammatory response that is pathogenic in inflammatory diseases. Because active cytokines amplify adaptive immunity through various mechanisms, IC 100, by attenuating cytokine activation, also attenuates the adaptive immune response. The lead indication for IC 100 is obesity with certain metabolic complications. To review a white paper summarizing the mechanism of action and preclinical data for IC 100, Click Here.

About ZyVersa Therapeutics, Inc.

ZyVersa (Nasdaq: ZVSA) is a clinical stage specialty biopharmaceutical company leveraging advanced proprietary technologies to develop first-in-class drugs for patients with inflammatory or kidney diseases with high unmet medical needs. We are well positioned in the rapidly emerging inflammasome space with a highly differentiated monoclonal antibody, Inflammasome ASC Inhibitor IC 100, and in kidney disease with phase 2 Cholesterol Efflux Mediator™ VAR 200. The lead indication for IC 100 is obesity and its associated metabolic complications, and for VAR 200, focal segmental glomerulosclerosis (FSGS). Each therapeutic area offers a "pipeline within a product," with potential for numerous indications. The total accessible market is over $100 billion. For more information, please visit www.zyversa.com.

Cautionary Statement Regarding Forward-Looking Statements

Certain statements contained in this press release regarding matters that are not historical facts, are forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995. These include statements regarding management's intentions, plans, beliefs, expectations, or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. ZyVersa Therapeutics, Inc ("ZyVersa") uses words such as "anticipates," "believes," "plans," "expects," "projects," "future," "intends," "may," "will," "should," "could," "estimates," "predicts," "potential," "continue," "guidance," and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions. Such forward-looking statements are based on ZyVersa's expectations and involve risks and uncertainties; consequently, actual results may differ materially from those expressed or implied in the statements due to a number of factors, including ZyVersa's plans to develop and commercialize its product candidates, the timing of initiation of ZyVersa's planned preclinical and clinical trials; the timing of the availability of data from ZyVersa's preclinical and clinical trials; the timing of any planned investigational new drug application or new drug application; ZyVersa's plans to research, develop, and commercialize its current and future product candidates; the clinical utility, potential benefits and market acceptance of ZyVersa's product candidates; ZyVersa's commercialization, marketing and manufacturing capabilities and strategy; ZyVersa's ability to protect its intellectual property position; and ZyVersa's estimates regarding future revenue, expenses, capital requirements and need for additional financing.

New factors emerge from time-to-time, and it is not possible for ZyVersa to predict all such factors, nor can ZyVersa assess the impact of each such factor on the business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. Forward-looking statements included in this press release are based on information available to ZyVersa as of the date of this press release. ZyVersa disclaims any obligation to update such forward-looking statements to reflect events or circumstances after the date of this press release, except as required by applicable law.

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Corporate, Media, and IR Contact:
Karen Cashmere
Chief Commercial Officer
kcashmere@zyversa.com
786-251-9641