AC Immune declares ACI-6758 intrabody as lead development candidate in its intracellular TDP-43-targeting program for ALS

- *ACI-6758 significantly reduced pathological pTDP-43 by up to 75% across multiple brain regions and improved motor function in a preclinical model of amyotrophic lateral sclerosis (ALS)*
- *In the preclinical model, neurofilament light chain (NfL), a clinically relevant biomarker of neurodegeneration in ALS, was reduced in the cerebrospinal fluid (CSF) supporting clinical translation*
- *ACI-6758 also reduced pathological phosphorylated TDP-43 (pTDP-43) by up to 98% in vitro while preserving physiological TDP-43 function*
- *Augments AC Immune's wider portfolio of assets targeting TDP-43, including its PET Tracer ACI-19626*

Lausanne, Switzerland, November 24, 2026 - AC Immune SA (NASDAQ: ACIU), a clinical-stage biopharmaceutical company targeting the key pathologic misfolded proteins and pathways that drive neurodegenerative diseases, today announced the selection of ACI-6758 as the lead development candidate in its TDP-43-targeting intracellular antibody (intrabody) program for amyotrophic lateral sclerosis (ALS).

Martin Zügel, interim CEO of AC Immune SA, commented: *"The progress in this TDP-43 program has again demonstrated the real strength of the science and innovation being conducted at AC Immune. TDP-43 represents a target of considerable interest as it is implicated as a co-pathology in multiple neurodegenerative diseases including Alzheimer's and Parkinson's disease, and as a driver of rare diseases such as ALS and frontotemporal dementia. The development of ACI-6758 complements our other TDP-43 targeting efforts including our TDP-43 PET tracer (ACI-19626) which has produced impressive results in a Phase 1 clinical study. Together they form a focused portfolio for the company with important opportunities for potential business development."*

The lead declaration is supported by *in vivo* results in the rNLS8 mouse model of ALS. Adeno-associated virus (AAV)-delivered ACI-6758 significantly reduced pTDP-43 pathology across several brain regions, with reductions of up to 75% (Figure 1). Total human TDP-43 levels were comparable between groups, supporting a pathology-selective mode of action. Furthermore, ACI-6758 improved motor function and reduced NfL levels in the CSF, supporting clinical translation.

In *in vitro* models, ACI-6758 demonstrated robust activity, reducing pathological pTDP-43 inclusions in neurons by up to 98%. Importantly, ACI-6758 did not interfere with the physiological function of TDP-43 in the splicing of several known targets, including STMN2, POLDIP3 and UNC13A. These data supported the selection of ACI-6758 over other non-pathology-selective TDP-43 candidates explored.

Francesca Capotosti, Senior Vice President Research at AC Immune SA, commented: *"The declaration of ACI-6758 as our TDP-43 intrabody lead candidate represents a significant milestone for the program and an important step forward for our intracellular targeting approach to treating neurodegenerative diseases. ALS remains a devastating disease with a huge unmet medical need. ACI-6758 combines selective targeting of pathological TDP-43 with preservation of its physiological function and clear in vivo activity, and we are confident that advancing the program into development is an important step toward helping patients affected by ALS."*

Damien Nevoltris, Group Leader, Antibody Engineering, and Project Leader, Research at AC Immune SA, commented: *"The pathological forms of TDP-43 are intracellular, creating major challenges for antibody-fragment delivery and stability inside cells. Our proprietary plug-and-play technology is designed to stabilize intrabodies, improve their expression, and enhance intracellular target engagement following gene therapy delivery. The fully humanized ACI-6758 has achieved the profile we were aiming for: selective recognition of an epitope associated with pathological TDP-43, no impact on physiological TDP-43 function, no immunogenicity predicted* in silico*, and clear* in vitro *and* in vivo *activity."*

ACI-6758 is intended for vectorized intracellular expression in the central nervous system. AC Immune is exploring translational studies to define the exposure required for efficacy and to inform the program's further

development. AC Immune's first-in-class TDP-43 PET tracer, ACI-19626, currently in Phase 1, will also support future in-human studies of ACI-6758.

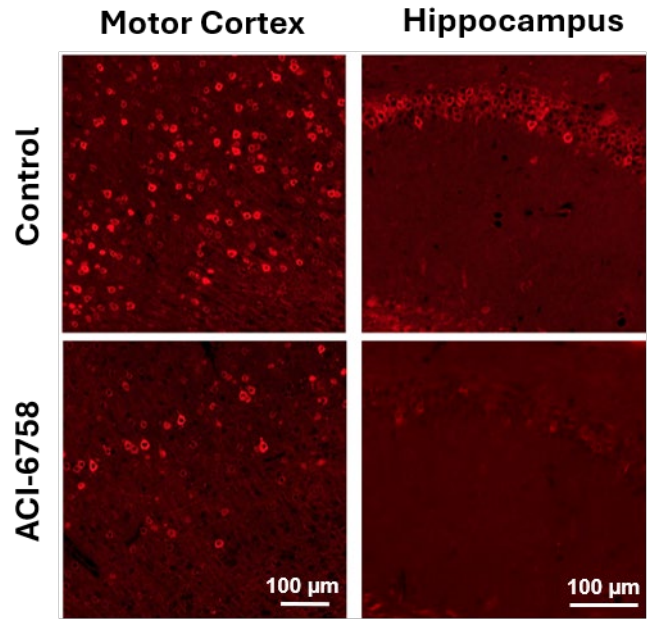


Figure 1. Representative images of pTDP-43 immunoreactivity in the motor cortex and hippocampus of rNLS8 ALS mice, 3 months after a single administration of ACI-6758 or vehicle. Red staining indicates pTDP-43.

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About ACI-6758

ACI-6758 is AC Immune's lead TDP-43-targeting intrabody candidate. It is a humanized single-chain variable fragment (scFv) antibody engineered for intracellular expression using AC Immune's proprietary charged-linker technology. It is designed to selectively bind pathological TDP-43 inclusions while sparing physiological nuclear TDP-43, a key requirement for addressing its toxic gain-of-function pathology without impairing its key physiological functions. The program combines AC Immune's antibody discovery capabilities with proprietary intrabody engineering designed to improve intracellular stability and enable targeting of disease-associated proteinopathies.

About TDP-43

TDP-43 is the major protein component of pathological inclusions in most cases of ALS and in a substantial proportion of frontotemporal dementia (FTD), and is also observed in other neurodegenerative diseases. Disease-associated TDP-43 mislocalizes from the nucleus and accumulates in the cytoplasm, where it can form pathological aggregates. Therapeutic strategies therefore need to address toxic pathological TDP-43 while preserving the normal nuclear functions of the protein.

About AC Immune SA

AC Immune (NASDAQ: ACIU) is a clinical-stage biopharma company selectively targeting the key pathologic misfolded proteins and pathways that drive neurodegenerative diseases. Building on more than two decades of expertise in the field of misfolded proteins, AC Immune is advancing a diversified portfolio of disease-modifying active immunotherapies and small molecule approaches.

AC Immune's wholly-owned pipeline includes its lead program, ACI-7104, in Phase 2 development for early Parkinson's disease (PD), a progressive neurodegenerative disease affecting c.10 million people worldwide with no approved disease-modifying therapies today. By targeting misfolded alpha-synuclein, a key driver of PD progression, ACI-7104 aims to slow, or halt, the spread of the disease throughout the brain before irreversible neurological damage occurs. The Company is also advancing ACI-19764, an NLRP3 inflammasome inhibitor in Phase 1, and a preclinical intracellular small molecule alpha-synuclein program.

AC Immune has built one of the most extensively validated neurodegenerative disease pipelines in biotech, including three active immunotherapies with FDA Fast Track designation, and programs being developed in collaboration with three of the world's leading pharmaceutical companies. These collaborations provide external validation of the Company's science, targets and proprietary platforms while contributing substantial non-dilutive funding, more than $4.5 billion in potential milestone payments, and future royalty opportunities. By combining deep expertise in protein misfolding with differentiated technology platforms and clinically validated targets, AC Immune is advancing a new generation of disease-modifying therapies for neurodegenerative diseases, aiming to make a real difference for patients.

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Forward looking statements

This press release contains statements that constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Forward-looking statements are statements other than historical fact and may include statements that address future operating, financial or business performance or AC Immune's strategies or expectations. In some cases, you can identify these statements by forward-looking words such as "may," "might," "will," "should," "expects," "plans," "anticipates," "believes," "estimates," "predicts," "projects," "potential," "outlook" or "continue," and other comparable terminology. Forward-looking statements are based on management's current expectations and beliefs and involve significant risks and uncertainties that could cause actual results, developments and business decisions to differ materially from those contemplated by these statements. These risks and uncertainties include those described under the captions "Item 3. Key Information – Risk Factors" and "Item 5. Operating and Financial Review and Prospects" in AC Immune's Annual Report on Form 20-F and other filings with the Securities and Exchange Commission. Forward-looking statements speak only as of the date they are made, and AC Immune does not undertake any obligation to update them in light of new information, future developments or otherwise, except as may be required under applicable law. All forward-looking statements are qualified in their entirety by this cautionary statement.